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Essential fatty acids in the prevention and/or treatment of depression in patients with coronary heart or artery disease

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(54) Title: ESSENTIAL FATTY ACIDS IN THE PREVENTION AND/OR TREATMENT OF DEPRESSION IN PATIENTS WITH CORONARY HEART OR ARTERY DISEASE

(57) Abstract: This invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω (3) docosahexaenoic acid (DHA) in the prevention and/or treatment of depression in patients with cardiovascular disease, such as coronary heart and/or coronary artery or vascular disease.

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ESSENTIAL FATTY ACIDS IN THE PREVENTION AND/OR TREATMENT OF DEPRESSION IN PATIENTS WITH CORONARY HEART OR ARTERY DISEASE

FIELD OF THE INVENTION

Essential fatty acids and compositions comprising thereof in the prevention and/or treatment of depression in patients with cardiovascular disease, such as coronary heart and/or coronary artery or vascular disease.

BACKGROUND OF THE INVENTION

In one aspect, this invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in the prevention and/or treatment of depression in patients with coronary artery disease.

It is well known that certain essential fatty acids contained in fish oil have a therapeutic effect in the prevention and treatment of cardiovascular disorders, such as in the treatment of hypertension, thrombosis, hypercholesterolemia, arteriosclerosis, cerebral infarction, prevention of sudden death in post myocardial infarction patients, improvement of endothelial function and hyperlipedemias.

US Patents US 5,502,077, US 5,656,667 and US 5,698,594 can be quoted as examples. The prevention of cardiovascular events, especially of mortality in patients who have survived the hospitalization phase of acute myocardial infarction (AMI) is described in the international patent application WO 00/48592.

The above prior art in particular provide knowledge about the utility of fatty acids belonging to the ω-3 family, more specifically (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA), in treating the above-mentioned disorders.

The fatty acid EPA, being a precursor of PGI3 and TxA3, exerts a preventing platelet aggregation effect and an antithrombotic effect that can be ascribed to inhibition of cyclooxygenase (similar effect to that of aspirin) and/or to competition with arachidonic acid for this enzyme, with consequent reduction in the synthesis of PGE2 and TxA2, which are well known platelet aggregating agents.

On the other hand the fatty acid DHA is the most important component of cerebral lipids in man and furthermore, being a structural component of the platelet cell it

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intervenes indirectly in increasing platelet fluidity, thus playing an important role in antithrombotic activity.

The international patent application WO 89/11521, whose description is herein incorporated by reference, describes in particular an industrial process for extracting mixtures with a high content in poly-unsaturated acids, including EPA and DHA and their ethyl esters, from animal and/or vegetable oils.

Mixtures of fatty acids, especially EPA/DHA, obtained according to WO 89/11521, are reported to be particularly useful in the treatment of cardiovascular diseases.

However, current methods of treatment used in human therapy have been shown to be insufficient in patients with coronary artery disease.

SUMMARY OF THE INVENTION

In one aspect, this invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in the prevention and/or treatment of depression in patients with cardiovascular disease, such as coronary heart, coronary artery or vascular disease.

In a further aspect of the invention there is provided a method for preventing and/or treating depression in a patient with cardiovascular disease comprising, administering to said patient a therapeutically effective amount of a medicament, wherein the medicament comprises as active ingredients a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), wherein:

a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5.

In yet another aspect of the invention there is provided the use of a therapeutically effective amount of a medicament comprising a high concentration mixture of EPA and DHA as active ingredients wherein:

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a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5,

and a pharmaceutically acceptable vehicle for the treatment of depression in patients with cardiovascular disease.

A still further aspect of the invention provides for the use of a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester as active ingredients in the preparation of a medicament useful for the prophylaxis and/or treatment of depression in patients with cardiovascular disease, wherein the medicament comprises as active ingredients a high concentration mixture of the essential fatty acids EPA and DHA, wherein:

a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5.

In another aspect of the invention there is provided use of a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester as active ingredients in the preparation of a medicament useful for the prophylaxis and/or treatment of depression in patients with cardiovascular disease, wherein the eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester concentration is greater than 25% b.w.

In one embodiment, the present invention provides a novel method for preventing and/or treating depression in patients with cardiovascular disease. In another embodiment, the patients have coronary heart and/or coronary artery or vascular disease. In yet another embodiment, the cardiovascular disease is coronary artery or vascular disease. The method of the present invention

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comprises administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a high content in eicosapentaenoic acid (EPA) ethyl ester, in docosahexaenoic acid (DHA) ethyl ester or in a high concentration mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. In one embodiment, the high concentration mixture comprises a high concentration mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester.

A high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, is to be understood to contain at least 20 % b.w. EPA-ethyl ester or DHA-ethyl ester, or at least 20% b.w. of a mixture of EPA-ethyl ester and DHA-ethyl ester.

In one aspect this invention pertains to the use of essential fatty acids containing a mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester in the prophylaxis and/or treatment of depression in patients with cardiovascular disease, in one example in patients with coronary heart and/or coronary artery or vascular disease, where the content in EPA-ethyl ester and DHA-ethyl ester in such mixture is greater than 25% b.w.

In another embodiment the invention provides a use of a therapeutically effective amount of essential fatty acids containing a high content in EPA-ethyl ester, in DHA-ethyl ester or a high concentration mixture thereof in the formation of a medicament for the treatment of cardiovascular disease, such as coronary heart and/or coronary artery or vascular disease.

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Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

The term "containing" or "comprising" as used herein is an inclusive and not exclusive term.

Recently new risk factors for coronary artery disease have been identified, among them depression. Major depressive disorders, as well as depression symptoms, are associated with higher rates of cardiovascular morbidity and mortality. Moreover, once the ischemic heart disease is established, the risk for suffering a fatal cardiac event is increased. Severe ventricular arrhythmias resulting in sudden cardiac death appear to be the leading cause of mortality in patients with depression. In addition, patients with anxiety and depressive disorders have been shown to have reduced heart rate variability. This finding may have important prognostic implications because low heart rate variability is a powerful predictor of sudden cardiac death. There is substantial evidence that major depression is associated with alterations in omega-3 acids status. A significant depletion of red cell membrane omega-3 fatty acids has been reported in major depression. Another study reported a negative correlation between with both, red blood cell membrane content of omega-3 fatty acids and dietary intake of these polyunsaturated fatty acids with severity of depression. Supplementation with EPA and DHA is known to increase the content of these unsaturated fatty acids in erythrocyte membranes. Studies in post-myocardial infarct patients have demonstrated that supplementation with DHA and EPA improves heart rate variability.

However, currently there are no efficacious and safe treatments known to prevent depression in patients with cardio-vascular disease and hardly other treatments of depression in patients with cardiovascular disease. One study with sertraline showed beneficial effects in post-myocardial patients with concomitant depression. It is well know that patients with cardiovascular diseases and depression are at a substantially increased risk of cardiovascular events and death.

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Therefore, there still is a substantial need for improved and effective prophylaxis and/or treatments with drugs, in particular for preventing these recurrences in patients with both, cardiovascular diseases and depression, and the effective treatment of depression in these patients. In one embodiment, the object of this invention, therefore, is to provide such improved and effective prophylaxis (preventing) and/or treatment of said patients with an effective drug, and in particular preventing the before mentioned recurrences in patients with both, cardiovascular diseases and depression, and/or treatment of depression in these patients.

In one aspect, this invention provides a novel method for preventing and/or treating depression in patients with cardiovascular disease. In one embodiment the cardiovascular disease is coronary heart and/or coronary artery or vascular disease. In another embodiment, the cardiovascular disease is coronary artery or vascular disease. In one embodiment, the method comprises administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a high content in eicosapentaenoic acid (EPA) ethyl ester, in docosahexaenoic acid (DHA) ethyl ester or in a high concentration mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. In one embodiment, a high concentration mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester is administered. The invention also provides a use of essential fatty acids such as a high concentration of EPA-ethyl ester, DHA-ethyl ester or mixture thereof for the prevention and treatment of depression in patients with cardiovascular disease.

A high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, is to be understood to contain at least 20 % b.w. EPA-ethyl ester or DHA-ethyl ester, or at least 20 % b.w. of a mixture of EPA-ethyl ester and DHA-ethyl ester.

In particular this invention pertains to the use of essential fatty acids containing a mixture of eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester in the prophylaxis and/or treatment of depression in patients with cardiovascular disease, in particular in patients with coronary heart and/or coronary artery or vascular disease, where the content in EPA-ethyl ester and DHA-ethyl ester in such mixture is greater than 25% b.w.

In one embodiment, an essential fatty acid with high content in EPA-ethyl ester or DHA-ethyl ester, according to the present invention, preferably contains more than 25%

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by weight (b.w.), in particular from about 60 to about 100% of such ester. These compounds can be obtained by known methods.

In an essential fatty acid with a high concentration mixture of EPA-ethyl ester and DHA-ethyl ester, preferably such a mixture has a content of EPA-ethyl ester and DHA-ethyl ester greater than 25% by weight, in particular from about 30 to about 100% by weight, preferably about 85% by weight. In the EPA-ethyl ester/DHA-ethyl ester mixture, EPA-ethyl ester preferably is present in a percentage from about 40 to 60% by weight and DHA-ethyl ester, preferably in a percentage from about 25 to about 45-50%. In any case the preferred EPA-ethyl ester/DHA-ethyl ester ratio by weight in such EPA-ethyl ester/DHA-ethyl ester mixture is about 0.9 to 1.5.

PHARMACOLOGY

Cardiovascular disease is the leading cause of morbidity and disability in the United States with an estimated 6 million people having symptomatic coronary heart disease.

Major depression is occurring at a younger age and a higher incidence than it used to be.

Alterations in phospholipids and cholesterol, which are structural components of all cell membranes in the brain, may induce changes in membrane microviscosity and, consequently in various neurotransmitter systems, which are thought to be related in the pathophysiology of depression, e.g. serotonin, and (nor-) adrenaline. Major depression and depressive symptoms, although commonly encountered in medical populations, are frequently under-diagnosed and untreated in patients with cardiovascular disease. In patients with coronary heart disease, the prevalence of major depression is nearly 20% and the prevalence of minor depression is approximately 27%. Depression (major depressive disorders as well as depressive symptoms) is associated with higher rates of cardiovascular morbidity. The prognosis after a coronary heart disease event is poorer in depressed patients than in non-depressed patients. Patients with depression are less likely to follow recommendation to reduce cardiac risk during recovery from a myocardial infarction. In major depression, there is a decreased ω-3 fractions in cholesterol esters and an increased C20:4ω 6/C20:5ω 3 ratio in cholesterol esters and phospholipids.

Depression is an important independent predictor of death after coronary artery bypass surgery. Survival analyses, controlling for age, sex, number of grafts, diabetes, smoking, left ventricular ejection fraction, and previous myocardial infarction, showed

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that patients with moderate to severe depression at baseline (adjusted hazard ration (HR) 2.4, p=0.001) and with mild or moderate to severe depression that persisted from baseline to 6 months (adjusted HR 2.2) had higher rates of death than did those without depression. Mild to moderate levels of depressive symptoms are also in patients after an acute myocardial infarction associated with decreased survival. Highest mortality rates were observed in patients with most severe depressive symptoms. However, compared with those without depression, higher mortality was also observed at very low levels of depressive symptoms not generally considered clinically significant. Increased mortality after a myocardial infarction is seen in both females and males. The 1-year cardiac mortality is approximately 3 times higher in depressed females and 2.5 times higher in depressed males than in non-depressed females, respectively non-depressed males. Preliminary research indicated that, in addition to the survival risks associated with post-myocardial depression, there are increased health care costs to both readmissions and out-patient contacts among depressed patients who survived the first post-myocardial infarction year. The reasons why patients with coronary heart disease and depression do have an increased mortality and morbidity are not quite known. However, there are indications that in depression there is an abnormal intake or metabolism of essential fatty acids in conjunction with decreased formation of cholesteryl esters. The arachidonic acid to eicosapentaeneoic acid ratio in blood correlates positively with the clinical symptoms of depression. Also a significant negative correlation is found between the EPA content in erythrocytes the severity of depression. Alterations in phospholipids and cholesterol, which are structural components of all cell membranes in the brain, may induce changes in membrane microviscosity and, consequently, in various neurotransmitter systems like in serotonin and (nor-) adrenaline. It is well known that these neurotransmitters play an important role in the pathophysiology of depression. Finally, the decreased food intake and weight loss, accompanying severe depression could lead to changes in fatty acid composition of serum phospholipids and cholesteryl esters, which could on their own affect membrane fluidity and inflammatory responses.

The efficacy of the treatment, according to the invention, is proven by indirect preclinical and clinical evidence:

1. Ingestion of large effects of ω-3 fatty acids is associated with a general dampening of signal transduction pathways associated with phosphatidylinositol, arachidonic acid, and other systems.

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2. DHA is involved in dopamine and serotonin metabolism in the developing rat brain.

3. Serotonergic and other neurochemical actions of ω-3 fatty acids in animals suggest anti-depressant activity.

4. Epidemiological data show that the national rates of major depression and bipolar disorder across different countries vary directly with fish consumption.

5. Epidemiological studies have demonstrated a correlation between plasma fatty acid composition and depression in the elderly.

6. In bipolar disorders, over-activity of cell signal transduction may be involved in the pathophysiology.

7. Patients with major depressive episodes showed a significant decrease in red blood cell membrane DHA and EPA levels.

8. Omega-3 fatty acids possess mood stabilizing effects in major depression and other neuropsychiatric disorders.

9. Addition of EPA to treatment resistant depression was associated with symptoms remission, structural brain changes and a reduced neuronal phospholipids turn-over.

10. Omacor, a high concentration mixture of EPA-ethyl ester and DHA-ethyl ester, does increase the red blood cell membrane EPA and DHA content.

The above mentioned evidence shows that the present invention provides a new and valuable therapeutic method for preventing and/or treating depression in patients with cardiovascular disease, in particular in patients with coronary heart and/or coronary artery or vascular disease. Accordingly, this invention provides a method for preventing and or treating depression in patients with coronary vascular disease, and in particular in patients with coronary heart and/or coronary artery or vascular disease, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

The essential fatty acid ethyl esters, according to the invention, can either have a high content, for instance more than 25% b.w., in EPA-ethyl ester or DHA-ethyl ester or in a mixture thereof. However, EPA-ethyl ester and DHA-ethyl ester are preferably present as a mixture thereof with a content of EPA-ethyl ester and DHA-ethyl ester higher

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than 25% b.w., in particular from about 30 to about 100% b.w., in one embodiment about 80%, 81%, 82%, 83%, 84%, or preferably about 85% b.w.

Based on the available evidence, according to a preferred aspect of the invention, the dosage of an essential fatty acid ethyl ester containing an EPA-ethyl ester and DHA-ethyl ester mixture with 85% b.w. titer for oral administration to a patient may vary from about 0.7 g to about 6 g daily, preferably about 1 g daily.

In one embodiment the high content EPA-ethyl ester, DHA-ethyl ester or high concentration mixture thereof is formulated into a capsule, such as a gel capsule, using methods known in the art.

In one embodiment, the gel capsule is a 1000 mg capsule. In another embodiment, said capsule comprises 90% b.w., ethyl esters of omega-3 fatty acids. In another embodiment, of said 90% b.w., in a 1000 mg capsule, about 465 mg is EPA-ethyl ester and about 375 mg is DHA-ethyl ester. In a further embodiment, said 1000 mg capsule comprises about 4 mg α-tocopherol in a suitable carrier (such as partially hydrogenated vegetable oils, including soybean oil), and other components of a gel capsule, such as gelatin, glycerol and purified water. In one embodiment of the invention, the dose provided is 4g per day of the 1000 mg capsule.

This amount of product as EPA-ethyl ester and DHA-ethyl ester mixture (or amount of EPA-ethyl ester alone or DHA-ethyl ester alone) may be administered in several divided doses throughout the day or preferably in a single administration, in order to achieve the desired hematic level. Obviously it is at the discretion of the physician to adjust the quantity of product to be administered according to the age, weight and general conditions of the patient. As such, "therapeutically effective amount" is an amount effective, at dosages and for periods of time necessary to achieve the desired therapeutic result. It is understood that such amount may vary according to factors such as disease state, age, sex and weight of the individual and the ability of a substance to elicit a desired response in an individual.

The medicament, e.g. in the form of a pharmaceutical composition, according to this invention can be prepared according to known methods in the art. The preferred route of administration is the oral one, however leaving alternative routes of administration, such as the parenteral route, to the discretion of the physician. The medicament or pharmaceutical composition can comprise the desired amount, e.g. a high content of EPA-ethyl ester, DHA-ethyl ester or high concentration mixture thereof in accordance with this

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invention and a pharmaceutical acceptable vehicle, e.g., carriers, excipients, adjuvants and buffers, for instance substances used in pharmaceuticals or known in the art, e.g., Remington's Pharmaceutical Sciences (Alfonso R. Gennaro ed. 18th edition 1990)

The variants of the present invention are furthermore defined in the sub-claims.

The following examples illustrate suitable formulations for oral administration, but do not intend to limit the invention in any way.

Gelatin capsules

According to known pharmaceutical techniques, capsules having the composition below and containing 1 g of active ingredient (EPA-ethyl ester and DHA-ethyl ester, 85% titer) per capsule are prepared.

Formulation 1

EPA-ethyl ester	525 mg / capsule
DHA-ethyl ester	315 mg / capsule
d-alpha tocopherol	4IU / capsule
gelatin	246 mg / capsule
glycerol	118 mg / capsule
red iron oxide	2.27 mg / capsule
yellow iron oxide	1.27 mg / capsule

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Formulation 2

Ethyl esters of polyunsaturated fatty acids with content in ethyl esters of w-3 poly-unsaturated esters (eicosapentaenoic EPA, docosahexaenoic DHA)	1000 mg 850 mg
d-1-α-tocopherol	0.3 mg
gelatin succinate	233 mg
glycerol	67 mg
sodium p-oxybenzoate	1.09 mg
sodium propyl p-oxobenzoate	0.54 mg

While the present invention has been described with reference to what is presently considered to be a preferred embodiment, it is to be understood that the invention is not limited to the disclosed embodiment. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for preventing and/or treating depression in a patient with cardiovascular disease comprising, administering to said patient a therapeutically effective amount of a medicament, wherein the medicament comprises as active ingredients a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), wherein:

a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5.

2. The method of claim 1, wherein the cardiovascular disease is selected from the group consisting of coronary heart and/or coronary artery or vascular disease.

3. The method of claim 1 or 2, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is at least 20% b.w.

4. The method of claim 1 or 2, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is at least 25% b.w.

5. The method according to claim 1 or 2, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is from about 30 to about 100% b.w.

6. The method according to claim 1 or 2, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is from about 30 to about 85% b.w.

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7. The method according to any one of claims 1 to 6, wherein the medicament is administered orally.

8. The method according to claim 7, wherein the medicament is administered orally at a dosage from about 0.7 g to about 6 g daily.

9. The use of a therapeutically effective amount of a medicament comprising a high concentration mixture of EPA and DHA as active ingredients wherein:

a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5,

and a pharmaceutically acceptable vehicle for the treatment of depression in patients with cardiovascular disease.

10. The use of claim 9, wherein the cardiovascular disease is coronary heart and/or coronary artery or vascular disease.

11. The use of claim 9 or 10, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is at least 20% b.w.

12. The use of claim 9 or 10, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is at least 25% b.w.

13. The use according to claim 9 or 10, wherein the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the mixture is from about 30 to about 100% b.w.

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14. The use according to claim 9 or 10, wherein the concentration in eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in such mixture is from about 30 to about 85% b.w.

15. The use according to any one of claims 9 to 14, wherein the medicament is administered orally.

16. The use according to claim 15, wherein the medicament is administered orally at a dosage from about 0.7 g to about 6 g daily.

17. Use of a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) as active ingredients in the preparation of a medicament useful for the prophylaxis and/or treatment of depression in patients with cardiovascular disease, wherein the medicament comprises as active ingredients a high concentration mixture of the essential fatty acids EPA and DHA, wherein:

a) EPA is present in the high concentration mixture in an amount of from 40 to 60% by weight;

b) DHA is present in the high concentration mixture in an amount of from 25 to 45-50% by weight; and

c) the EPA/DHA ratio in the high concentration mixture is from 0.9 to 1.5.

18. The use of claim 17, wherein the cardiovascular disease is selected from the group consisting of coronary heart and/or coronary artery or vascular disease.

19. Use according to claim 17 or 18, wherein the high concentration mixture of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester is greater than 25% b.w.

20. Use according to any one of claims 17 to 19, wherein the concentration in eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in such mixture is from about 30 to about 100% b.w.

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21. Use according to any one of claims 17 to 19, wherein the concentration in eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in such mixture is about 85% b.w.

22. Use according to any one of claims 17 to 21, wherein the medicament is for oral administration.

23. Use according to claim 22, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 6 g daily.

24. A method for preventing and/or treating depression in a patient with cardiovascular disease according to claim 1, substantially as hereinbefore described with reference to the Formulations.

25. Use of a high concentration mixture of the essential fatty acids eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester as active ingredients in the preparation of a medicament according to claim 9, substantially as hereinbefore described with reference to the Formulations.

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