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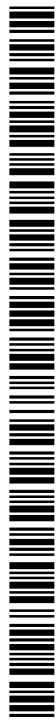


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**WO 2004/078166 A2**

(54) Title: USE OF OMEGA-3-FATTY ACIDS IN THE TREATMENT OF DIABETIC PATIENTS

(57) Abstract: The invention concerns the use of essential fatty acids with a high content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) useful for preventing of cardiovascular events in patients with diabetes mellitus.

## Use of Omega-3-Fatty Acids in the Treatment of Diabetic Patients

## DESCRIPTION

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 (20:5 $\omega$  3) eicosapentaenoic acid (EPA) and (22:6 $\omega$  3) docosahexaenoic acid (DHA) in patients who suffer from diabetes.

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 hyperlipidemias.

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  $\omega$ -3 family, more specifically (20:5 $\omega$  3) eicosapentaenoic acid (EPA) and (22:6 $\omega$  3) docosahexaenoic acid (DHA), in treating the above-mentioned disorders.

The fatty acid EPA, being a precursor of PGI<sub>3</sub> and TxA<sub>3</sub>, 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 PGE<sub>2</sub> and TxA<sub>2</sub>, 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 inter-

venes indirectly in increasing platelet fluidity, thus playing an important role in anti-thrombotic 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 who have a diabetes mellitus, in particular in those patients in whom it is desired to also prevent cardiovascular events. It is well known that patients with diabetes, in particular with diabetes mellitus, are at a substantially increased risk of cardiovascular events and death.

Therefore, there still is a substantial need for improved and effective treatments with drugs, in particular for preventing these recurrences. Object of this invention, therefore, is to provide such improved and effective treatment of diabetic patients.

This invention, therefore, suggests the novel use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for the treatment of patients suffering from diabetes. In particular, the invention is directed to preventing cardiovascular events in patients who have diabetes mellitus.

For ease of description "EPA-ethyl ester" and "DHA-ethyl ester" will be also quoted here as "EPA" and "DHA".

In particular this invention pertains to the use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for the treatment of patients suffering from diabetes, preferably for preventing cardiovascular events in patients who have diabetes, where the content in EPA and DHA in such mixture is greater than 25% b.w.

An essential fatty acid with high content in EPA or DHA, according to the present invention, preferably contains more than 25% 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 and DHA, preferably such mixture has a content in EPA and DHA greater than 25% by weight, in particular from about 30 to about 100% by weight, preferably about 85% by weight.

In the EPA/DHA mixture, EPA preferably is present in a percentage from about 40 to 60% by weight and DHA, preferably in a percentage from about 25 to about 45-50%. In any case the preferred EPA/DHA ratio in such EPA/DHA mixture is about 0.9/1.5.

#### PHARMACOLOGY

Diabetes mellitus has become an increasingly prevalent disease worldwide. The prevalence of diabetes is increasing rapidly and the number of individuals with type II diabetes (80-90% of all diabetic people) is depicted to reach 300 million in the year 2025, accounting for 5.4% of the global population. Furthermore, cardiovascular events are important contributors to morbidity and mortality in patients with diabetic disease. The risk of death from cardiovascular disease is in patients with diabetes two to six times that among persons without diabetes. Currently, over 50% of diabetic patients die from coronary heart disease. In contrast to non-diabetic people, coronary heart mortality has not declined in diabetic people. Type II diabetes eliminates the protective advantage of female sex against coronary heart disease mortality. The prognosis after a coronary heart disease event is poorer in diabetic people than in non-diabetic people. Within 1 year after an acute myocardial infarction, 44.2% of type II diabetic men and 36.9% of type II diabetic women die.

All manifestations of coronary heart disease are at least twice as common in patients with diabetes as in non diabetic individuals. Moreover, recently close interrelations between diabetes and cardiovascular disease, not at least with coronary artery disease, were elucidated. It has been demonstrated in a number of studies that 28% of patients with known coronary artery disease have diabetes, and as many as 70% of patients with acute coronary syndromes have abnormal glucose metabolism, either in the form of diabetes or impaired glucose tolerance. Major risk factors for coronary heart disease in patients with diabetes are:

1. unfavorable lipoprotein profile, characterized by increased serum triglycerides;
2. elevated blood pressure;

3. predisposition to formation of thrombosis, including the following manifestations:  
high concentrations of plasminogen activator-1 and cytokines;
4. impairment of endothelin-dependent vasodilatation;
5. cardiac autonomic impairment leading to decreased ischaemic pain perception, higher heart rate and decreased heart rate variability, which in turn increases the risk for sudden death.

The efficacy of the treatment, according to the present invention, is proven by ample pre-clinical and clinical evidence:

1. EPA plus DHA induces a reduction in the levels of triglycerides and of very-low density lipoprotein cholesterol (VLDL) in patients with hypertriglyceremia;
2. EPA plus DHA does lower blood pressure in patients with hypertension;
3. Dietary EPA and DHA down-regulate gene expression of platelet-derived growth factor-A and of platelet-derived growth factor-B in human mononuclear cells;
4. Supplementation with EPA plus DHA mitigates the course of coronary atherosclerosis in patients with coronary heart disease;
5. EPA and DHA improves endothelial function in heart transplant recipients.
6. Experimental studies have shown that EPA and DHA are antiarrhythmic in several animal models, probably due to specific modulation of ion currents;
7. EPA and DHA increases heart rate variability in healthy volunteers and in survivors of a myocardial infarction;
8. EPA plus DHA decreases the incidence of sudden death in survivors of a myocardial infarction.

The above mentioned evidence of reducing risk factors shows that the present invention provides a new and valuable therapeutic tool for treating diabetic patients, and in particular for preventing cardiovascular events in diabetic patients.

Accordingly, this invention also provides a method for treating diabetic patients, preferably patients with diabetes mellitus and in particular for preventing cardiovascular events in diabetic patients, preferably in patients with diabetes mellitus, 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 acids, according to the invention, can either have a high content, for instance more than 25% b.w., in EPA or DHA or in a mixture thereof. However, EPA

and DHA-ethyl ester are preferably present as a mixture thereof with a content in EPA and DHA higher than 25% b.w., in particular from about 30 to about 100% b.w., 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 containing an EPA and DHA mixture with 85% b.w. titer for oral administration to a patient may vary from about 0.7g to about 6g daily, preferably about 1g daily.

This amount of product as EPA and DHA mixture (or amount of EPA alone or DHA 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.

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

The following examples illustrate preferred 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 1g of active ingredient (EPA and DHA, 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

**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- $\alpha$ -tocopherol	0.3 mg
gelatin succinate	233 mg
glycerol	67 mg
sodium p-oxybenzoate	1.09 mg
sodium propyl p-oxobenzoate	0.54 mg

## CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for the treatment of patients suffering from diabetes, preferably for preventing cardiovascular events in patients who have diabetes, where the content in EPA and DHA in such mixture is greater than 25% b.w.
2. Use according to claim 1, wherein the medicament is useful for preventing cardiovascular events in a patient who has diabetes mellitus.
3. Use according to claim 1 or 2, wherein the content in EPA and DHA in such mixture is from about 30 to about 100% b.w.
4. Use according to claim 1 or 2, wherein the content in EPA and DHA in such mixture is about 85% b.w.
5. Use according to anyone of claims 1 to 4, wherein the medicament is for oral administration.
6. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 6 g daily.
7. Use according to claim 6, wherein the EPA and DHA ration in the EPA and DHA mixture is about 0.9/1.5.
8. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for the treatment of patients suffering from diabetes, preferably for preventing cardiovascular events in patients who have diabetes, wherein the EPA and DHA content is greater than 25% b.w.
9. Use according to claim 8, wherein the medicament is useful for preventing cardiovascular events in a patient who has diabetes mellitus.
10. Use according to claim 8 or 9, wherein the EPA or DHA content is from about 60 to about 100% b.w.

11. Use according to anyone of claims 8 to 10, wherein the medicament is for oral administration.
12. A method for the treatment of patients suffering from diabetes, preferably diabetes mellitus, in particular for preventing cardiovascular events in patients who have diabetes, preferably in a patient who has diabetes mellitus, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) wherein the content in EPA and DHA in such mixture is greater than 25% b.w.
13. A method according to claim 12, wherein the content in EPA and DHA in such mixture is from about 30 to about 100% b.w.
14. A method according to claim 12, wherein the content in EPA and DHA in such mixture is about 85% b.w.
15. A method according to claim 12, 13 or 14, wherein the medicament is administered orally.
16. A method according to claim 14, wherein the medicament is administered orally at a dosage from about 0.7g to about 6 g daily.
17. A method according to claim 16, wherein the EPA / DHA ratio in the EPA and DHA mixture is about 0.9/1.5
18. A method for the treatment of patients suffering from diabetes, preferably diabetes mellitus, in particular for preventing cardiovascular events in patients who have diabetes, preferably in a patient who has diabetes mellitus, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), wherein the content in EPA and DHA in such mixture is greater than 25% b.w.
19. A method according to claim 18, wherein the content in EPA and DHA in such mixture is from about 30 to about 100% b.w.

20. A method according to claim 18, wherein the content in EPA and DHA in such mixture is about 85% b.w.

21. A method according to claim 18, 19 or 20, wherein the medicament is administered orally.

22. A method according to claim 20, wherein the medicament is administered orally at a dosage from about 0.7g to about 6 g daily.

23. A method according to claim 22, wherein the EPA / DHA ratio in the EPA and DHA mixture is about 0.9/1.5.

24. A method for the treatment of patients suffering from diabetes, preferably diabetes mellitus, in particular for preventing cardiovascular events in patients who have diabetes, preferably in a patient who has diabetes mellitus, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or in docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

25. A method according to claim 24, wherein the content EPA or DHA is from about 60 to about 100% b.w.

26. A method according to claim 24 or 25, wherein the medicament is administered orally.

27. A method for the treatment of patients suffering from diabetes, preferably diabetes mellitus, in particular for preventing cardiovascular events in patients who have diabetes, preferably in a patient who has diabetes mellitus, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

28. A method according to claim 27, wherein the content in EPA or DHA is from about 60 to about 100% b.w.

29. A method according to claim 27 or 28, wherein the medicament is administered orally.