Title: USE OF A FATTY ACID COMPOSITION FOR TREATMENT OF MALE INFERTILITY

Abstract: The invention relates to a fatty acid composition comprising (all-6 omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-2 omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition or a dietary foodstuff for prevention or treatment of male infertility. The present invention also relates to a method for treatment of male infertility by using said fatty acid composition.
USE OF A FATTY ACID COMPOSITION FOR TREATMENT OF MALE INFERTILITY

Technical field of the invention

The invention comprises a number of aspects. According to a first aspect of the present invention, a use of a pharmaceutical composition for prevention or treatment of male infertility, is disclosed. According to a second aspect of the invention, a use of a pharmaceutical composition for prevention or treatment of asthenozoospermia, is disclosed. According to a third aspect of the present invention, a use of a pharmaceutical composition for prevention or treatment of teratozoospermia, is disclosed. According to a fourth aspect of the invention, a use of a pharmaceutical composition for prevention or treatment of a condition due to decreased concentration of DHA in sperm, is disclosed. Moreover, according to a fifth aspect of the invention, a use of a dietary foodstuff for non-medical prevention or treatment of male infertility, is disclosed. According to a sixth aspect of the present invention, a use of a dietary foodstuff for non-medical prevention or treatment of asthenozoospermia, is disclosed. According to a seventh aspect of the invention, a use of a dietary foodstuff for non-medical prevention or treatment of teratozoospermia, is disclosed. According to eighth aspect of the present invention, a use of a dietary foodstuff for non-medical prevention or treatment of a condition due to decreased concentration of DHA in sperm, is disclosed.

Further, according to a ninth aspect of the invention, a method for prevention or treatment of male infertility, is disclosed. According to a tenth aspect of the present invention, a method for prevention or
treatment of asthenozoospermia, is disclosed. According to the eleventh aspect of the invention, a method for prevention or treatment of teratozoospermia, is disclosed. Finally, according to the twelfth aspect of the present invention, a method for prevention or treatment of a condition due to decreased concentration of DHA in sperm, is disclosed.

The aspects above are based on at least one of the following features: a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, or a fatty acid composition comprising at least one of EPA or DHA, to be administered to a human or an animal together with DHA in the case where the composition comprises EPA, or EPA in the case where the composition comprises DHA, wherein the total administered amount of DHA is ≥ EPA.

Background of the invention

Male infertility is responsible for approximately 45% of childless couples' inability to achieve pregnancy and no certain method of improving male fertility exists. In recent years the prognosis for infertile couples has improved but mainly by manipulation of the female such as better ways of optimising the time for conception or artificial fertilisation in uteri or in vitro. Poor sperm-forward motility (asthenozoospermia) and low number of sperm are considered to be the most common findings in infertile men with pathologic morphology (teratozoospermia) being the third most common feature. A meta-analysis of published scientific studies during the last 50 years including 14,947 men showed a significant decrease in sperm concentration during this period [Becker S and Berhane K. A meta-analysis of 61 sperm count studies revisited. Fertile Sterile 1997;67:1103-1108]. Other studies have confirmed this finding indicating that sperm concentration has decreased by 0.8%
yearly in the US and 2.35% in Europe during the same interval [Carlsen E, et al. Evidence for decreasing quality of semen during the past 50 years. BMJ 1992;305:609-613]. Histology of testis tissue obtained by autopsy supports the fact that the number of men with normal spermiogenesis is declining [Pajari J, et al. Incidence of disorders of spermatogenesis in middle aged Finnish men, 1981-91: two necropsy series. BMJ 1997;314:13-18]. The reason for this alarming finding is not known but older age by the time of family building, a dramatic change in dietary habits especially in the intake of fat, and exposition to environmental pollution have been discussed. There is certainly need for a treatment alternative for the infertile man.

Description of prior art

Production of sperms takes place in the Leydig cells of the testicles. Their development from diploid stem cells into mobile, haploid sperm is governed by several hundred genes in which the cell nucleus becomes the sperm head while portions of the Golgi, mitochondrial, and cytoplasmic material become the tail and the sheet. The tail and head each have distinctive functions where the tail is responsible for movement in the epididymis and, after ejaculation, in the female genital tracts. The head with its acrosome plays an important role in capacitation and the acrosome reaction that renders the sperm capable of fusing with the egg plasma membrane, penetrating the egg for fertilisation and transferring the genetic material.

The protein components of sperm heads and tails have been characterised in detail [Holger H, et al. The protein complexity of the cytoskeleton of bovine and human sperm heads. Exp Cell Res 1995;218:174-182] but certain lipids also seem to play an important role in the constitution and function of sperms. Great differences in the composition of sterols, fatty acids, and the
phospholipid molecular species between heads and tails have been observed in monkeys [Connor WE, et al. Uneven
distribution of desmosterol and docosahexaenoic acid in
the heads and tails of monkey sperm. J Lipid Res
1998;39:1404-1411]. As these lipids have an important
role in membrane integrity, fluidity, stability, and
permeability, these differences in membrane lipid
composition may contribute to the unique functions of the
sperms. The most striking difference between heads and
tails were in the concentration of the omega-3 fatty acid
docosahexaenoic acid (DHA, 22:6n-3)). Over 99% of the DHA
was localised in the tails. The reason for this selective
accumulation of DHA is not known but since high
concentrations of DHA in cell membranes are correlated
with membrane fluidity it is possible that this selective
concentration of a polyunsaturated fatty acid (PUFA) in
the tail is necessary to provide for the bending and
flexing for motility of sperms. In fact it has been found
that the concentration of DHA in monkey testis increased
greatly during puberty suggesting the importance of this
fatty acid for the maturation of sperms [Connor WE, et
al. Biochemical marker for puberty in monkey testis. J
Clin Endocrin Metab 1997;82:1911-1916]. In fertile
humans PUFA’s counted for about 34% of total fatty acids
and DHA contributed to more than 60% of total PUFA’s
[Zalata AA, et al. The fatty acid composition of
phospholipids of spermatozoa from infertile patients. Mol
Hum Reprod 1998;4:111-118].

DHA is the most unsaturated fatty acid of the omega-
3 series with 6 double bonds (Fig. 1). The omega-3 fatty
acids are essential to animals and humans meaning that
they have to be provided in the diet. In humans the
omega-3 fatty acid with the shortest chain length alfa-
linolenic acid (ALA, 18:3n-3) may be converted to DHA
through the intermediate eicosapentaenoic acid (EPA,
20:5n-3, Fig. 1) by means of elongation and desaturation
proposed by Sprecher (Fig. 2) The enzyme delta-6-
desaturase is the rate-limiting enzyme and the conversion rate from ALA is slow in humans.

It has been reported that the capacity of the delta-6-desaturase enzyme is reduced by age and high intake of fat in the diet. Interestingly the conversion rate of EPA to DHA is much higher indicating another mechanism of desaturation than the delta-6 route.

As mentioned previously high age and dietary factors have been claimed as possible factors for reduced male fertility and if DHA is important for the genesis and function of sperms, delta-6-desaturase insufficiency could be the factor responsible for male infertility, at
least in people not eating fatty fish containing DHA. Seldom intake of fish is a common dietary habit throughout the Western World today.


Due to the extreme unsaturation of DHA the molecule is readily oxidised. Oxidative damage of DHA has been suggested as another mechanism for low DHA concentration with possibly reduction of sperm viability [Ottero M, et al. Variation of docosahexaenoic acid content in subsets of human spermatozoa at different stages of maturation: implication for sperm lipoperoxidative damage. Mol Reprod & Devel 2000;55:326-334, Zalata AA, et al. White blood cells cause oxidative damage to the fatty acid composition of phospholipids of human spermatozoa]. Increased oxidative stress is a regular finding in elderly and individuals having a too low intake of anti-oxidative food like fruit and vegetables.

In a previous study [Penny PC, et al. Boar fertility and reproductive performance: enhancement by fatty acid manipulation of spermatozoa. ISSFAL 2000 (abstract) P-7-
51] male breeding pigs were fed a selection of dietary supplements base on combination of different fatty acids with a high concentration of DHA together with anti-oxidants. The DHA concentration of the sperms increased significantly together with sperm number and motility. Based on these data it was believed that DHA supplementation could be used to increase the content of DHA in testicles of infertile men to improve sperm quality. To test this hypothesis a placebo-controlled study was initiated randomly allocating 28 healthy asthenozoospermic individuals to treatment with 400mg/d, 800mg/d or placebo [Conquer JA, et al. Effect of DHA supplementation on DHA status and sperm motility in asthenozoospermic males. Lipids 2000; 35:149-154]. Each group was treated for a period of 3 months. Semen and blood samples were collected prior to and after the 3-month treatment period.

The fatty acid profile in plasma and seminal plasma of all three groups were similar at study entry. Supplementation with DHA in both groups resulted in an increased content of DHA in plasma. However, DHA in seminal plasma did not increase or increased only slightly, the difference compared to pre-treatment levels not reaching statistical significance. The DHA content of the sperms did not change in the three groups. Furthermore, DHA supplementation had no effects on sperm motility or sperm concentration.

Moreover, in WO 9966877 a method and a dietary supplement for increasing fertility in an animal is presented. The method comprising feeding the animal a omega-3 fatty acid containing component, which omega-3 fatty acid containing component is preferably of plant, animal or single cell oil origin.

Summary of the invention

Based on the present invention a number of aspects are presented in the appended claims. These aspects are;
1. Use of a pharmaceutical composition for prevention or treatment of male infertility.

2. Use of a pharmaceutical composition for prevention or treatment of asthenozoospermia.

3. Use of a pharmaceutical composition for prevention or treatment of teratozoospermia.

4. Use of a pharmaceutical composition for prevention or treatment of a condition due to decreased concentration of DHA in sperm.

5. Use of a dietary foodstuff for non-medical prevention or treatment of male infertility.

6. Use of a dietary foodstuff for non-medical prevention or treatment of asthenozoospermia.

7. Use of a dietary foodstuff for non-medical prevention or treatment of teratozoospermia.

8. Use of a dietary foodstuff for non-medical prevention or treatment of a condition due to decreased concentration of DHA in sperm.


12. Method for prevention or treatment of a condition due to decreased concentration of DHA in sperm.

The aspects above are based on at least one of the following features;

- a fatty acid composition comprising at least (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1.

- a fatty acid composition comprising at least one of EPA or DHA, to be administered to a human or
an animal together with DHA in the case where the composition comprises EPA, or EPA in the case where the composition comprises DHA, wherein the total administered amount of DHA is ≥ EPA.

According to a first aspect of the invention, the invention relates to the use of a fatty acid composition comprising at least (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (hereafter abbreviated EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (hereafter abbreviated DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of male infertility.

According to a second aspect of the present invention, the invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of asthenozoospermia.

According to third aspect of the invention, the invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of teratozoospermia.

According to the fourth aspect of the invention, the invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of a condition due to decreased concentration of DHA in sperm.

In another embodiment, the prevention or treatment of male infertility includes especially prevention or
treatment of male infertility due to at least one of asthenozoospermia, teratozoospermia, and a decreased concentration of DHA in sperm or any combinations of these conditions.

Moreover, the effect of the invention is accomplished by the combination of at least the two fatty acids EPA and DHA, wherein the amount of DHA is ≥ EPA. As described in the prior art, DHA itself had no effect on sperm motility or sperm concentration, but the administration of a fatty acid composition according to the invention comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA is 1:X, where X is ≥ 1, showed a surprisingly synergetic effect. Moreover, from the research leading to the invention a most preferred effect of the invention is accomplished by a fatty acid composition rich in DHA, but still containing at least EPA. The term rich herein includes a fatty acid composition there the amount (weight or volume) of DHA is equal or larger than EPA.

An advantage of the invention is that intake of a pharmaceutical composition according to the invention increases the possibilities for many men to improve their sperm motility, increase the amount of sperms respectively increase the concentration of DHA in their sperm, which will help more childless couples to achieve pregnancy.

In an other embodiment of the invention a pharmaceutical composition comprising at least EPA is to be administered together with DHA, and then the pharmaceutical composition comprising at least DHA, EPA is to be administered together with DHA, wherein the total administered amount of DHA is ≥ EPA, in both cases for prevention or treatment of male infertility, especially male infertility due to at least one of asthenozoospermia, teratozoospermia, a decreased concentration of DHA in sperm or any combinations of
these conditions. Further, preferably the EPA and the DHA may be administered subsequently to each other.

In a preferred embodiment of the invention, the fatty acid composition is administered to a human. The pharmaceutical composition according to the invention is preferably intended to be administered to humans, but the invention also relates to use of a pharmaceutical composition according to the invention that may be administered to animals, preferably animals such as domestic animals, livestock and/or cattle.

Moreover, in another embodiment of the invention the fatty acid composition is obtained from at least one of vegetable, microbial and animal or combinations thereof.

In a preferred embodiment of the invention the EPA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof, and the DHA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof. Namely, it is possible that DHA and EPA may independently of each other come from different origins.

In a preferred embodiment of the invention, at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil.

In a more preferred embodiment of the invention both DHA and EPA is obtained from fish oil.

In another embodiment of the invention, the fatty acid composition is presented in at least one of esterified form, ethyl ester form, salt form and free acid form, or any combinations thereof.

In preferred embodiments of the invention, the fatty acid composition comprises at least DHA and EPA in the forms of triglycerides, re-esterified triglycerides with content of di- and mono-glycerides, ethyl esters, salts and/or free fatty acids or any combinations of the above mentioned forms. The rest of the fatty acid composition is preferably comprised of omega-3-fatty acids other than DHA and EPA that have 20-22 carbon atoms in any of the
above mentioned forms. For instance, the fatty acid composition may additionally also comprise at least one of arachidonic acid (ARA), docosapentaenoic acid, heneicosapentaenoic acid and octadecatetraenoic acid.

In another embodiment, the combination of EPA:DHA are present in the composition in an EPA:DHA ratio from about 1:1 to 1:6. In a specific preferred embodiment of the invention, the weight ratio of EPA:DHA in the fatty acid composition is about 1:6.

In another embodiment of the invention, 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA. Preferably, 60% to 80% by weight of the fatty acid composition is constituted by EPA and DHA. In a specific preferred embodiment about 60% by weight of the fatty acid composition is constituted by a combination of EPA and DHA.

In a preferred embodiment of the invention, the fatty acid composition also comprises (all-Z omega-3)-7,10,13,16,19-docosapentaenoic acid (DPA), in an amount of about 10% to 40% of the amount of DHA in the composition. Moreover, in another embodiment of the present invention, the fatty acid composition being administered in amount providing a daily dosage of 0.5g to 6.0g of said fatty acid composition, preferably between 2g and 4g, to a human or an animal.

In a preferred embodiment of the invention the pharmaceutical composition or pharmaceutical preparation or medicinal product may preferably be produced for oral administration in the form of for instance a pill, a soft capsule or the like. However, the pharmaceutical composition or pharmaceutical preparation or medicinal product may also be produced for administration through any other route where the active ingredients may be efficiently absorbed and utilized, e.g. intravenously, subcutaneously, intramuscularly, intranasally, rectally, vaginally or topically.
The pharmaceutical composition according to the invention may also comprise other substances, in addition to the EPA and DHA active ingredients, such as vehicle, one or more acceptable carrier, fillers, stabilizers, extenders, binders, humidifiers, surfactants, lubricants etc., which all are well known to persons skilled in the art. In addition, one or more pharmaceutical acceptable antioxidants, for example hydroxytoluene, butyrate, quinone, tocopherol, ascorbic acid etc., preservatives, colouring agents, perfumes, flavourings and other pharmaceutically agents may be used. The same substances as mentioned above is also valid for a dietary foodstuff according to the invention.

According to a fifth aspect of the present invention, the invention relates to the use of a fatty acid composition comprising at least \((\text{all-}Z\ \omega-3)-5,8,11,14,17\)-eicosapentaenoic acid (EPA) and \((\text{all-}Z\ \omega-3)-4,7,10,13,16,19\)-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is \(1:X\), where \(X \geq 1\), for the manufacture of a dietary foodstuff for non-medical prevention or treatment of male infertility.

According to a sixth aspect of the invention, the invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is \(1:X\), where \(X \geq 1\), for the manufacture of a dietary foodstuff for non-medical prevention or treatment of asthenozoospermia.

According to a seventh aspect of the invention, the invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is \(1:X\), where \(X \geq 1\), for the manufacture of a dietary foodstuff for prevention or treatment of teratozoospermia.

According to a eighth aspect, the present invention relates to the use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA
in the fatty acid composition is 1:X, where X is ≥ 1, for
the manufacture of a dietary foodstuff for non-medical
prevention or treatment of a condition due to decreased
concentration of DHA in sperm

5 In a preferred embodiment, the invention relates to
a dietary foodstuff comprising a mixture containing at
least EPA and DHA, wherein the amount of DHA ≥ EPA, for
non-medical prevention or treatment of male infertility,
especially male infertility due to asthenozoospermia,
teratozoospermia, low DHA concentration in sperm or
combinations of these conditions.

10 The effect of the invention is also here
accomplished by the use and administration of a fatty
acid composition comprising at least a combination of EPA
and DHA, wherein the weight ratio of EPA:DHA in the fatty
acid composition is 1:X, where X is ≥ 1. As described in
prior art, dietary supplementation of DHA itself cannot
be used to prevent or treat the conditions mentioned
above, but administration of EPA and DHA together or in
combination, wherein the amount of DHA is equal or larger
than EPA, has a surprisingly synergistic effect.

15 An advantage of manufacturing and selling a dietary
foodstuff according to the invention for prevention
and/or treatment of male infertility, especially male
infertility due to asthenozoospermia, teratozoospermia,
low DHA concentration in sperm or any combinations of
these conditions, is that such a dietary product will be
more easily accessible for men around the world. They
preferably can buy the product or supplement in a health
food store and/or a supermarket, and don’t need to visit
a doctor in the first place.

20 In another embodiment of the invention, the dietary
foodstuff according to the invention is produced in such
way that the EPA part of the composition is separate from
the DHA part of the composition. In this case, an EPA-
containing composition is to be administered together
with DHA and a DHA-containing composition is to be
administered together with EPA, but still the total administered amount of DHA is equal or larger than the amount of EPA. Preferably, the EPA and the DHA may be administered subsequently to each other. As mentioned before, the weight ratio of EPA:DHA is also here 1:X, where X is equal or larger than 1. Please note that X being one of an integer or non-integer. Further, the dietary foodstuff according to the invention is preferably intended to be administered to humans, but it may also be administered to animals, preferably animals such as domestic animals, livestock and cattle.

In another embodiment of the invention the fatty acid composition is obtained from at least one of vegetable, microbial and animal or combinations thereof.

In a preferred embodiment, at least one of EPA and DHA is obtained from at least one of vegetable, microbial and animal origins or any combinations thereof. Further, DHA and EPA may independently of each other come from different origins. In a more preferred embodiment at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil. In a most preferred embodiment of the invention both DHA and EPA is obtained from fish oil.

In preferred embodiments of the invention, the dietary foodstuff comprising a mixture containing at least a fatty acid composition comprising EPA and DHA, wherein the amount of DHA is ≥ EPA, and DHA and EPA is at least in one of the form of triglycerides, re-esterified triglycerides with content of di- and mono-glycerides, ethyl esters, salts, free acids or in any combinations thereof. The rest of the fatty acid composition is preferably comprised of omega-3-fatty acids other than DHA and EPA that have 20-22 carbon atoms in any of the above mentioned forms, preferably arachidonic acid (ARA) in any of the above mentioned forms.

In another embodiment of the invention, the fatty acid composition may additionally also comprise at least
one of arachidonic acid (ARA), docosapentaenoic acid, heneicosapentaenoic acid and octadecatetraenoic acid.

In another embodiment of the present invention, 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA. Preferably, 60% to 80% by weight of the fatty acid composition is constituted by EPA and DHA. In a specific preferred embodiment of the invention, the weight ratio of EPA:DHA in the fatty acid composition is about 1:6.

In a specific preferred embodiment about 60% by weight of the fatty acid composition is constituted by a combination of EPA and DHA. For instance, a cod-liver oil or a tuna fish-liver oil may be used.

In a preferred embodiment of the invention, the fatty acid composition also comprises (all-Z omega-3)-7,10,13,16,19-docosapentaenoic acid (DPA), in an amount of about 10% to 40% of the amount of DHA in the composition.

In another embodiment of the invention, the fatty acid composition being administered in amount providing a daily dosage of 0.5g to 6.0g of said fatty acid composition, preferably between 2g and 4g.

In a preferred embodiment, the dietary foodstuff is in form of a gelatine capsule, which capsule is flavoured. Moreover, preferably the active compounds according to the dietary foodstuff of the invention may be administered in one of the possible forms and ways as mentioned before for the pharmaceutical composition according to the invention. In addition, the dietary foodstuff according to the invention may comprise, in addition to the EPA and DHA ingredients, at least one of the same substances as mentioned before according to a pharmaceutical composition, but also other suitable agents such as vitamins and/or minerals.

According to a ninth aspect of the invention, the invention relates to a method for prevention or treatment of male infertility, wherein a therapeutically active
amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

According to a tenth aspect of the invention, the invention relates to a method for prevention or treatment of asthenozoospermia, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

According to an eleventh aspect of the invention, the invention relates to a method for prevention or treatment of teratozoospermia, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

According to a twelfth aspect of the invention, the invention relates to a method for prevention or treatment of a condition due to decreased concentration of DHA in sperm, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment. In another embodiment, the invention relates to a method for prevention and/or treatment of male infertility, especially male infertility due to asthenozoospermia, teratozoospermia, decreased concentration of DHA in sperm or combinations of these conditions, wherein a therapeutically or pharmaceutically active amount of at least a fatty acid composition comprising EPA and DHA, wherein the amount of DHA is ≥ EPA, is administrated to a patient in a need of the mentioned treatment. The effect of the invention is accomplished by preferably the combination of the two
fatty acids EPA and DHA, but the amount of DHA may be equal or larger than EPA.

In another embodiment of the invention a therapeutically or pharmaceutically active amount of a fatty acid composition comprising at least EPA is to be administered together with DHA, and then the composition comprising at least DHA, EPA is to be administered together with DHA, wherein the total administered amount of DHA is ≥ EPA, in both cases for prevention or treatment of male infertility, especially male infertility due to at least one of asthenozoospermia, teratozoospermia, a decreased concentration of DHA in sperm or any combinations of these conditions.

In another embodiment of the invention, at least one of EPA and DHA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof. In a preferred embodiment of the invention, at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil.

In a preferred embodiments of the invention, the therapeutically or pharmaceutically active amount of a fatty acid composition comprising at least EPA and DHA is administrated to a patient, wherein the DHA and EPA is in one of the forms of triglycerides, re-esterified triglycerides with content of di- and mono-glycerides, ethyl esters, salts, free acids or any combinations thereof. The rest of the fatty acid composition is preferably comprised of omega-3-fatty acids other than DHA and EPA that have 20-22 carbon atoms in any of the above mentioned forms.

In another embodiment of the invention, 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA. In a preferred embodiment of the invention, 60% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

In another embodiment of the invention, the fatty acid composition also comprises (all-Z omega-3)-
7,10,13,16,19-docosapentaenoic acid (DPA), in an amount of about 10% to 40% of the amount of DHA in the composition. Moreover, in another embodiment of the invention, the pharmaceutically or therapeutically active composition is administered in amount providing a daily dosage of 0.5 to 6.0 grams of the fatty acid composition according to the invention.

In a preferred embodiment of the invention the fatty acid composition is administered in a daily dosage of 2 to 4g and most preferably about 3g.

In a preferred embodiment of the invention, the pharmaceutically active composition is administered in a daily dosage comprising about 450-850 mg EPA and about 1.7-3.0 g DHA. In a specific preferred embodiment of the invention the dosage of EPA is about 0.8 g and the dosage of DHA is about 1.9 g.

In a preferred embodiment, the pharmaceutically active compound according to the invention is administered in a food product or as a dietary foodstuff.

The analysis in % by weight is based on the ethyl esters even if other derivatives of salts or the acids themselves are a part of the present invention.

Definitions

As used herein the term manufacture is interpreted to include production of a pharmaceutical composition and/or a medicinal product. Moreover, as used herein the term asthenozoospermia means poor sperm forward motility. Further, as used herein the term pharmaceutical means pharmaceutical preparations and/or compositions and medical food. A pharmaceutical preparation according to the present invention may also comprise other substances such as an inert vehicle or a pharmaceutically acceptable adjuvance, carriers, preservatives etc., which all are well-known to those skilled in the art.

As used herein, the term dietary foodstuff is interpreted to include food and food supplement to
animals and/or humans, fortification of food, dietary supplement, functional food and nutrient supplement.

As used herein the term patient relates to any human or non-human mammal in need of treatment with the medicinal product or method according to the invention.

As used herein, the term marine oil includes oil from fish, seals, cetaceans, sea shell and sea mammals. Non limiting examples of fish oil is e.g. Menhaden oil, Cod Liver oil, Herring oil, Capelin oil, Sardine oil, Anchovy oil and Salmon oil. The fish oils mentioned above may be recovered from fish organs, e.g. cod liver oil, as well as from the meat of the fish.

As used herein, the term microbial oils also includes “single cell oils” and blends, or mixtures, containing unmodified microbial oils. Microbial oils and single cell oils are those oils naturally produced by micro organisms during their lifespan.

As used herein, the term treatment means both treatment having a curving or alleviating purpose and treatment having a preventive purpose. The treatment can be made either acutely or chronically. Treatment can be given to both humans and animals. Non-limiting examples of such animals is e.g. domestic animals, livestock and cattle.

As used herein, the term prevention means actions having a preventive purpose to prevent a condition to appear. Preventive actions can be given to both humans and animals.

Brief description of the drawings

In the studies and examples below reference is made to the accompanying drawings, where all figures concern studies performed on human. The studies were preformed in order to demonstrate improved sperm motility and morphology in fertile men. Herein, reference is made to accompanying drawings, on with:
Figure 3 shows the levels (%) of DHA in plasma total phospholipid.  
Figure 4 shows the levels (%) of DHA in sperm total phospholipid.  
Figure 5 shows the effect on sperm motility.  
Figure 6 shows the effect on abnormal morphology.  
Figure 7 shows the relationship between total sperm count (mill) and DHA (%) in sperm total phospholipid. Finally, figure 8 shows the relationship between DHA (%) in sperm total phospholipid and DHA (%) in plasma total phospholipides.

Example

The invention will now be further explained in the following examples. The examples are only intended to illustrate the invention and should in no way be considered to limit the scope of the invention.

Study 1

In order to evaluate the effect of a fatty acid composition according to the present invention on male infertility, 16 asthenozoospermia men, aged 30-40 years and living in the Reykjavik, Island, area, with sperm motility lower than 30% of normal value volunteered to participate in an open intervention using a 60% of weight omega-3 concentrate from fish. The concentrate (EPAX 2050TG) contained 20% eicosapentaenoic acid (EPA) and 50% docosahexaenoic acid (DHA) as re-esterified triglyceride with a triglyceride content of 50-55%, diglyceride content of 40-45% and monoglyceride content of about 5%. Namely, a fatty acid composition comprising at least EPA and DHA, wherein the amount of DHA is larger than EPA, was used. The participants had not consumed any other omega-3 preparation or cod liver oil at least two years prior to the trial. They did not use medication and none were heavy smokers or drinkers.
Blood and semen samples were collected two weeks before study start (A), the day the trial started (B), at 10 weeks (C) and at 20 weeks (D) after study start. After completion of the study, the participants were controlled after two (E) and 10 weeks (F). All together the participants were controlled six times. The frequent controls were warranted to compensate for anticipated large variations in study parameters. During the treatment period, the participants were given six capsules of the omega-3 concentrate daily, each capsule containing 750 mg oil, during 20 weeks. The daily dose of EPA was 0.81 g and DHA 1.89 g. The following parameters were measured for each sample: Sperm count, sperm motility, sperm morphology, semen viscosity, fatty acid composition of sperm phospholipids, fatty acids in blood plasma and lipid peroxides.

The study shows that the supplementation with a fatty acid composition comprising at least EPA and DHA, wherein the amount of DHA is larger than EPA, increases the average concentration of DHA in the plasma phospholipids, as evident from figure 3. Moreover, the distribution of the amount of DHA in sperm phospholipidies in patients at study start, after 10 weeks and 20 weeks of treatment respectively 10 weeks after the completion of the study, is shown in figure 4. The best effect seems to be obtained after 10 weeks of treatment.

Moreover, it should be pointed out that participants with the best sperm motility (least pathological values) at study entry demonstrated an improvement in sperm motility from pre-study values to values during treatment, as evident from figure 5. The positive values were retained also after the study. The administration of the fatty acid composition did not show an effect on those participants with the poorest motility before study start.

In addition, abnormal sperm morphology was reduced during treatment and the positive effects were retained
after completion of the study, as seen in fig 5. The best results were obtained two weeks after completion of the study. Normal morphology increased concomitantly with the best values two weeks after study completion.

This result shows that treatment with a fatty acid composition according to the invention increases the possibilities for many men to improve their sperm motility, increase the amount of sperms respectively increase the concentration of DHA in their sperm, which will help more childless couples to achieve pregnancy.

Study 2

In this study, the relationship between total sperm count (mill) and DHA (%) in sperm total phospholipid and the relationship between DHA (%) in sperm total phospholipid and DHA (%) in plasma total phospholipid for three participants were studied. Herein, participants one and three were non-smokers, and participant 2 was a smoker. The study was carried out in the same way as mentioned in study 1 and the participants were given the same fatty acid composition, a fatty acid composition rich in DHA compared to EPA. Samples were collected two weeks before study start, the day the trial started, at 10 weeks and at 20 weeks after study start. After completion of the study, the participants were controlled after two and 10 weeks. All together the participants were controlled six times.

Figure 7 shows that the total sperm count (mill) is correlated to the level (%) of DHA in sperm total phospholipid. In participants one and three the treatment with a fatty acid composition according to the invention had an effect on the DHA level of sperm total phospholipid as well as the sperm count. Moreover, figure 8 illustrates the relationship between DHA (%) in sperm total phospholipid and DHA (%) in plasma total phospholipid after 20 weeks of treatment according to the invention.
Discussion

The result shows that treatment with a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, improved sperm motility and morphology in infertile men. Moreover, the DHA concentrations increased in almost every participant. These findings are unexpected and differ significantly from the previous study in humans using DHA alone. From animal and human studies it is documented that DHA is enriched in sperms and that infertile men are deprived of sperm DHA. Based on prior art and the present study it is obvious that DHA supplementation alone cannot increase sperm DHA and normalise sperm motility and morphology.

Thus, a fatty acid compositions according to the present invention are potentially valuable for the treatment and prophylaxis of male infertility or multiple factors with influence on male infertility, such as asthenozoospermia, teratozoospermia, low concentration of DHA or the like.

The doses of the composition of this invention needed for therapeutic or prophylactic effect will vary with the type of administration, body size, and the seriousness of the condition to be treated.

It is advantageous that the compositions according to the present invention are being well tolerated, not giving any severe side effects.

Example of pharmaceutical preparation

Soft gelatine capsules containing 0.75 g/capsule in prepared. Composition:

- EPA: 180 mg/capsule
- DHA: 420 mg/capsule
- Covitol F-1000: 3 mg/capsule
- Coviox T-70: 1.1 mg/capsule
- Tocopherol: 4 mg/capsule
The rest of the fatty acid composition is preferably essentially comprised of omega-3-fatty acids other than DHA and EPA that have 20-22 carbon atoms in any of the above mentioned forms, preferably at least DPA.

The capsule may be micro- or macro encapsulated. Further, the capsule may be constituted by one of bovine gelatine, fish gelatine or pig gelatine. Alternatively, a vegetable capsule may be used.

The active ingredients and the excipients are weighed an homogenized on a high speed stirrer. The mixture is then colloid milled and deitated in a stainless steel vessel ready for encapsulation. The mixture is filled in soft gelatine capsules of size 20 oblong (average weight 1.2 g) using a standard capsule machine.

The invention shall not be limited to the above shown embodiments and examples, but shall be interpreted within the scope of the appending claims.
1. Use of a fatty acid composition comprising at least (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of male infertility.

2. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of asthenozoospermia.

3. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of teratozoospermia.

4. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a pharmaceutical composition for prevention or treatment of a condition due to decreased concentration of DHA in sperm.

5. Use of a fatty acid composition comprising at least one of EPA or DHA, for the manufacture of a pharmaceutical composition to be administered to a human or an animal together with DHA in the case where the composition comprises EPA, or EPA in the case where the composition comprises DHA, wherein the total administered amount of DHA is ≥ EPA, for prevention or treatment of male infertility.

6. Use according to any of the claims 1-4, wherein the fatty acid composition is administered to a human or an animal.
7. Use according to any of the claims 1-5, wherein at least one of EPA and DHA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof.

8. Use according to any of the claims 1-5, wherein at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil.

9. Use according to any of the claims 1-5, wherein the fatty acid composition is presented in at least one of esterified form, ethyl ester form, salt form and free acid form, or any combinations thereof.

10. Use according to any of the claims 1-4, wherein 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

11. Use according to any of the claims 1-4, wherein 60% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

12. Use according to any of the claims 1-5, wherein the fatty acid composition also comprises (all-3)-7,10,13,16,19-docosapentaenoic acid (DPA), in an amount of about 10% to 40% of the amount of DHA in the composition.

13. Use according to any of the claims 1-4, wherein said fatty acid composition being administered in amount providing a daily dosage of 0.5g to 6.0g of said fatty acid composition, preferably between 2g and 4g.

14. Use of a fatty acid composition comprising at least (all-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a dietary foodstuff for non-medical prevention or treatment of male infertility.

15. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for
the manufacture of a dietary foodstuff for non-medical prevention or treatment of asthenozoospermia.

16. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a dietary foodstuff for prevention or treatment of teratozoospermia.

17. Use of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, for the manufacture of a dietary foodstuff for non-medical prevention or treatment of a condition due to decreased concentration of DHA in sperm.

18. Use of a fatty acid composition comprising at least one of EPA or DHA, for the manufacture of a dietary foodstuff to be administered to a human or an animal together with DHA in the case where the composition comprises EPA, or EPA in the case where the composition comprises DHA, wherein the total administered amount of DHA is ≥ EPA, for prevention or treatment of male infertility.

19. Use according to any of the claims 14-17, wherein the fatty acid composition is administered to a human or an animal.

20. Use according to any of the claims 14-18, wherein at least one of EPA and DHA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof.

21. Use according to any of the claims 14-18, wherein at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil.

22. Use according to any of the claims 14-18, wherein the fatty acid composition is presented in at least one of esterified form, ethyl ester form, salt form and free acid form, or any combinations thereof.
23. Use according to any of the claims 14-17, wherein 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

24. Use according to claim 23, wherein 60% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

25. Use according to any of the claims 14-17, wherein said fatty acid composition being administered in amount providing a daily dosage of 0.5g to 6.0g of said fatty acid composition, preferably between 2g and 4g.

26. Use according to any of the claims 14-18, wherein the fatty acid composition also comprises (all-Z omega-3)-7,10,13,16,19-docosapentaenoic acid (DPA), in an amount of about 10% to 40% of the amount of DHA in the composition.

27. Use according to any of the claims 14-17, wherein the dietary food stuff is in form of a gelatine capsule, which capsule is flavoured.

28. A method for prevention or treatment of male infertility, wherein a therapeutically active amount of a fatty acid composition comprising at least a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA), wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

29. A method for prevention or treatment of asthenozoospermia, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

30. A method for prevention or treatment of teratozoospermia, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.
acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

31. A method for prevention or treatment of a condition due to decreased concentration of DHA in sperm, wherein a therapeutically active amount of a fatty acid composition comprising at least EPA and DHA, wherein the weight ratio of EPA:DHA in the fatty acid composition is 1:X, where X is ≥ 1, is administrated to a patient in a need of said treatment.

32. A method for prevention or treatment of male infertility, wherein a therapeutically active amount of a fatty acid composition comprising EPA or DHA is administrated together with DHA in the case where the composition comprises EPA, or EPA in the case where the composition comprises DHA, wherein the total administered amount of DHA is ≥ EPA, to a patient in a need of said treatment.

33. Method according to any of the claims 28-32, wherein at least one of EPA and DHA is obtained from at least one of vegetable, microbial and animal origins or combinations thereof.

34. Method according to any of the claims 28-32, wherein at least part of the EPA and/or the DHA is produced from a marine oil, preferably a fish oil.

35. Method according to any of the claims 28-32, wherein the fatty acid composition is presented in at least one of esterified form, ethyl ester form, salt form and free acid form, or any combinations thereof.

36. Method according to any of the claims 28-31, wherein 15% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

37. Method according to any of the claims 28-31, wherein 60% to 80% by weight of the fatty acid composition is comprised of EPA and DHA.

38. Method according to any of the claims 28-32, wherein the fatty acid composition also comprises (all-Z omega-3)-7,10,13,16,19-docosapentaenoic acid (DPA), in an
amount of about 10% to 40% of the amount of DHA in the composition.

39. Method according to any of the claims 28-32, wherein said composition is administered orally, intravenously, subcutaneous, rectally, vaginally, and/or topically to a patient such as a human or an animal.

40. Method according to any of the claims 28-32, wherein said composition being administered in amount providing a daily dosage of 0.5g to 6.0g of said fatty acid composition, preferably between 2g and 4g.

41. Method according to any of the claims 28-32, wherein said composition is administered in a food product or as a dietary foodstuff.
Effect of treatment with a fatty acid composition comprising at least EPA and DHA, wherein the amount of DHA ≥ EPA, on DHA (%) in sperm total phospholipid

**Fig. 3**

Effect of treatment with a fatty acid composition comprising at least EPA and DHA, wherein the amount of DHA ≥ EPA, on DHA (%) in sperm total phospholipid

**Fig. 4**
Good motility

Effect on sperm motility

Fig. 5

Abnormal morphology

Effect on abnormal morphology

Fig. 6
Relationship between total sperm count (mill) and DHA (%) in sperm total phospholipid.

**Fig. 7**

Relationship between DHA (%) in sperm total phospholipid and DHA (%) in plasma total phospholipid after 10 weeks of treatment.

**Fig. 8**
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/557, A61K 35/60, A61P 15/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM.ABS.DATA, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 9966877 A2 (AGRICULTURAL RESEARCH ORGANIZATION), 29 December 1999 (29.12.1999), see example 5</td>
<td>1-41</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
7 May 2004

Date of mailing of the international search report
19-05-2004

Name and mailing address of the ISA/Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer
Carolina Gómez Lagerlöf/ELY
Telephone No. +46 8 782 25 00

Form PCT/IB/210 (second sheet) (January 2004)
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6, 19, 28–41
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.
Claims 6,19,28-41 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv).
Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
<table>
<thead>
<tr>
<th>WO</th>
<th>Document Number</th>
<th>Date</th>
<th>AU</th>
<th>Document Number</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO</td>
<td>9966877</td>
<td>29/12/1999</td>
<td>IL</td>
<td>4530299 A</td>
<td>10/01/2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>125097 A</td>
<td>12/01/2003</td>
</tr>
<tr>
<td>WO</td>
<td>0197802</td>
<td>27/12/2001</td>
<td>AU</td>
<td>7423201 A</td>
<td>02/01/2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EP</td>
<td>1292295 A</td>
<td>19/03/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GB</td>
<td>0014758 D</td>
<td>00/00/0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GB</td>
<td>2363331 A,B</td>
<td>19/12/2001</td>
</tr>
</tbody>
</table>