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(54) Title: VITAMIN MIXTURES

(57) Abstract: The present invention relates to a vitamin composition that strengthens and promotes retinal health, in particular in people being affected with AMD.



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VITAMIN MIXTURES

The present invention relates to a vitamin composition that strengthens and promotes retinal health through the prevention, stabilization, reversal and/or treatment of visual acuity loss in people with certain ocular diseases.

More specifically, the present invention relates to an antioxidant , omega-3-fatty acids and lutein supplement composition that decreases visual acuity loss by reducing the risk of developing age-related macular degeneration (AMD). It further relates to an antioxidant, omega-3-fatty acids, chromium and selenium composition. It also relates to an antioxidant , omega-3-fatty acids, chromium, selenium and zinc composition. Moreover, said compositions typically exhibit a favorable role in other chronic pathologies of the eye such as retinitis pigmentosa.

As used herein, an antioxidant is selected from vitamin E, vitamin C, beta-carotene and lutein and mixtures thereof. In a preferred aspect, beta-carotene is omitted from these antioxidants.

The present invention likewise provides a method of treating / preventing a human or other animal suffering from AMD or being at risk of developing AMD comprising administering an effective amount of any of the compositions disclosed herein.

The compounds of the invention can be administered by oral, intraperitoneal, intravenous, subcutaneous, transcutaneous or intramuscular routes. A preferred route of administration is the oral route.

Accordingly, it is an object of the present invention to provide a pharmaceutical composition effective in the prevention, stabilization, reversal and/or treatment of macular degeneration and/or visual acuity loss, and/or some other retinal diseases (e.g. retinitis pigmentosa) in particular in accordance to all specified examples and claims of the present disclosure.

The following detailed description is provided to enable any person skilled in the art to which the present invention pertains to make and use the same, and sets forth the best mode contemplated by the inventors of carrying out the subject invention.

The preferred vitamin composition of the present invention is a formulation of essential ingredients preferably in quantities set forth below in Table 1, to be ingested daily.

Table 1

Ingredient (preferred source)	A preferred daily dosage (e.g. in one capsule) and typical deviation there from in weight percent	Typical Total Daily Dosage Ranges
Beta-carotene (natural)	2 mg (3344 IU); (+/- 20%)	0.5 – 6 mg (836 – 10002 IU)
Ascorbic Acid (vitamin C)	60 mg; (+/- 20%)	10 – 150 mg
Vitamin E (D, L- tocopheryl-acetate (natural)	10 mg (10 IU); (+/- 20%)	5 – 30 mg
Zinc (e.g. zinc gluconate / zinc citrate/ acetate/chloride/ lactate/oxide / sulfate)	15 mg; (+/- 20%)	5 – 45 mg
Selenium (e.g. sodium selenite)	50 micrograms; (+/- 20%)	15 – 150 micrograms
Chromium (e.g. chromium-(III)-trichloride hexahydrate)	25 micrograms; (+/- 20%)	5 – 75 micrograms
Lutein (pure Flora Glo)	6 mg; (+/- 20%)	1 – 20 mg
Omega 3 fatty acid (e.g. fish oil 33% eicosapentaenoic acid (EPA) : 22% docohexaenoic acid (DHA)	200 mg ; (+/- 20%)	10 – 600 mg

The preferred daily dosage of the subject composition as specified above may be administered in the form of one or more tablets. Most preferably the daily dosage of the subject composition is provided in the form of one tablet taken three times daily, for a total of 3 tablets a day, or in the form of 1 tablets taken twice daily, for a total of 2 tablets a day. Compared to taking the total daily dose once a day, twice or three times daily dosing in one or more tablets per dose provides improved absorption and better maintenance of blood levels of the essential ingredients.

Tablets of the preferred formulation of the subject composition may contain larger or smaller quantities of essential ingredients per tablet than the minimum quantities per tablet specified above.

Larger quantities of essential ingredients, to compensate for some degradation which may occur over time. Smaller quantities of essential ingredients, for example, to take into account the food intake situation of a patient / animal.

Typically, the listed quantities of ingredients as contained in a composition of the present invention may typically range from 20 % below the indicated quantities of each ingredient up to 20% above the indicated quantities of each ingredient. Therefore, as used herein, an addressed concentration shall encompass +/- 20% by weight of an addressed and listed ingredient. For illustration purposes, 10 mg vitamin E shall for example encompass a range from 8 – 12 mg vitamin E.

By providing larger quantities of essential ingredients in each tablet, one is ensured that even with ingredient degradation, one hundred percent of the ingredient amount specified on the tablet sale label is provided upon oral administration of the tablet through to the specified expiration date of the tablet. Another consideration in formulating the subject composition is that depending on the source and/or manufacturing process of the individual ingredients, individual ingredient degradation rates may vary. For example, depending on the source of beta-carotene, a quantity of approximately 5 to 10 percent more beta-carotene may be necessary per tablet to provide the specified amount of beta-carotene per tablet as that listed on the tablet sale label through to the expiration date of the product. Accordingly, the specific formulation of the subject composition will vary depending on the sources of the individual ingredients and the specified length of product shelf life before expiration.

Typically, the product shelf life for nutritional or dietary supplements is approximately two to three years. Tablet formulations may also vary somewhat depending on slight deviations from manufacturing specifications within controlled tolerance ranges as customary within the field of art. Hence, typically a deviation of + / - 20% (smaller / larger) amounts in a preferred composition are still suitable to exhibit a pharmacological efficacy.

Variations contemplated in administering the subject composition to humans or other animals include, but are not limited to, providing time-release tablets or tablets manufactured to be administered as a single dose or as other multiple part dosages. Additionally, alternative avenues of administration besides oral administration are contemplated herein such as for example, but not limited to, intraperitoneal, intravenous, subcutaneous, sublingual, transcutaneous, intramuscular or like forms of administration.

The preferred route of administration is the oral route. Each tablet of the subject composition preferably contains the following essential ingredients in the quantities specified below including overages to compensate for ingredient degradation. For purposes of simplicity

only, formulations of the subject composition are provided below in accordance with a 3-tablet oral daily dosage regime.

As used herein the term a tablet does also pertain to a capsule, drageé, pellet, suppository and the like. Hence the term tablet pertains in particular to the quantity contained in one respective piece.

VITAMIN C

Vitamin C is a well known water-soluble antioxidant. Humans depend on external sources of vitamin C to meet their vitamin C requirements. Vitamin C in the form of ascorbate is found in the aqueous humor of human eyes.

Vitamin C typically protects the retina against the side effects of light.

The U.S. recommended dietary allowance (RDA) for vitamin C in the form of ascorbic acid is 60 mg.

The subject composition provides a daily dose of preferably 60 mg of vitamin C.

Ascorbic acid is the preferred source of vitamin C in the subject tablets, although other sources such as for example sodium ascorbate could alternatively be used.

In a preferred aspect a pharmaceutical composition of the present invention contains 60 mg vitamin C per tablet.

On a total daily dosage vitamin C is typically present in an amount of from 10 - 150 mg, more preferably from 30 – 100 mg, and in particular from 40 – 80 mg.

VITAMIN E

Vitamin E is also a well-known antioxidant. Vitamin E can work synergistically with vitamin C in protecting vital cell function from normal oxidants. The DHA supplementation of the present invention requires supplementation in Vitamin E that plays a protective role on the membranous lipids. Vitamin E is a relatively non-toxic fat-soluble vitamin. Vitamin E is readily oxidized thereby significantly reducing its activity during periods of storage prior to ingestion. Once ingested, vitamin E is stored within the body and can contribute to the total body pool of vitamin E for up to one year.

Preferably the subject composition provides approximately 10 mg of vitamin E per tablet.

DL-alpha tocopheryl acetate is the preferred source of vitamin E in the subject tablets although other sources of vitamin E, such as for example trimethyl tocopheryl acetate and/or vitamin E succinate, may be used in the alternative.

1.0 mg of vitamin E is equal to 1 IU of dl-alpha tocopheryl acetate. Alternatively, 1mg D alpha tocopheryl acetate corresponds to 1.5 IU.

On a total daily dosage vitamin E is typically present in an amount of from 5 – 30 mg, especially from 7 – 20 mg, and in particular from 10 – 15 mg.

ZINC

Zinc is important in maintaining the health of an eye's retina and is an essential part of more than 100 enzymes involved in digestion, metabolism, reproduction and wound healing. The RDA for zinc is approximately 10 mg.

Zinc plays an antioxidant role as a cofactor for enzymes that directly participate in oxidant defense.

Zinc concentrations in the retina and choroid are among the highest in the body .

Zinc is also considered to have an interaction with vitamine A in the generation of the visual pigments of the retina.

Studies have shown that Zinc slows visual field loss in AMD patients.

Preferably, the subject composition provides approximately 15 mg zinc per tablet.

Zinc is preferred in the form of zinc oxide in subject tablets due to the fact zinc oxide provides the most concentrated form for elemental zinc and is well tolerated in the digestive system. However, other forms of zinc such as for example zinc gluconate, zinc citrate, zinc acetate, zinc chloride, zinc lactate, or zinc sulfate may alternatively be used or be used in combination with zinc oxide in the subject composition. As used herein, zinc refers to a zinc salt, and more preferably to zinc oxide, zinc chloride or zinc gluconate, most preferably to zinc gluconate.

On a total daily dosage zinc is typically present in an amount of from 5 – 45 mg, more preferably from 10 – 40 mg, and in particular from 25 – 35 mg.

Chromium

As used herein, chromium refers to a Cr^{3+} - salt. A preferred chromium salt is chromium trichloride hexahydrate, chromium sulfate or chromium oxide, and more preferably chromium trichloride hexahydrate.

Chromium is in particular important for two reasons :

for oxidative balance

for insulinemia balance , diabetes is often associated to AMD

Moreover, chromium, like zinc, is another important cofactor for metalloenzymes,.

Chromium, e.g. in the form of chromium trichloride hexahydrate is preferably used in a composition of the present invention. Other chromium salts might be used as well, such as e.g. sulfate, oxide and the like.

Preferably the subject composition provides approximately 25 micrograms of chromium per tablet.

On a total daily dosage, chromium may typically be present in an amount of from 5 – 75 micrograms, more preferably from 10 – 50 micrograms, and especially from 20 – 40 micrograms.

LUTEIN

Lutein, like beta-carotene, is a carotenoid. Lutein is also an antioxidant found in the retina of healthy eyes.

Lutein and zeaxanthine are xanthophylls, belonging to the group of carotinoids.

Lutein and zeaxanthine are pigments found in retina; mostly in the macula area, where they play a filter role from blue light and probably an anti oxidant role. These pigments are not synthesized in vivo, thus an external (food) supplementation is required for the macular pigment composition.

Lutein is the precursor of zeaxanthin.

Epidemiologic studies suggests that lutein consumption might be inversely related to eye diseases such as AMD. Studies in human show that lutein supplementation results in increased macular pigment.

It appears that the supplementation of 6 mg /day decreases the AMD incidence. Therefore, the subject composition preferably provides approximately 6 mg of pure lutein per tablet.

Lutein in the form of pure Flora Glo (supplier Roche) is preferably used. This source provides crystalline lutein and zeaxanthin, from marigold oleoresins extracted from marigold flowers (tagetes). Lutein, zeaxanthin and other carotenoids represent, according to their label, 80 % of the weight of the raw material called "FloraGLO crystalline Lutein". This is taken into account when provided in a composition of the present invention.

Preferably an addressed composition contains approximately 1 - 20 mg, more preferably 2 – 17 mg, and even more preferably 3 – 14 mg lutein per day.

OMEGA-3-FATTY ACIDS

Fatty acids from the omega 3 group are mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids modify for example the composition with respect to the membranous permeability. They may also modify the distribution of membranous proteinic receptor.

Thus the protective role of DHA towards AMD appears to result from different mechanisms: improve the rhodopsine (retinal pigment) regeneration at the par pigmentary epithelium - photoreceptor level

play a role in the setting up of a lipid background that would improve the rhodopsine activity.

DHA may impart further effects to the retina, namely :

direct positive effect on the structure and the maintenance of lipid balance of external photoreceptors segments.

anti-apoptotic action

anti oxidant action

increase mitochondrial activity

Preferred examples of omega-3-fatty acids are docohexaenoic acid (DHA) or eicosapentaenoic acid (EPA).

The maximum dosage recommended for EPA / DHA supplementation is for example 300 mg / kg (Simopoulos et al.Conference report : workshop on the essentiality of and recommended dietary intakes for omega -6- and omega-3-fatty acids. J Am Coll Nutr, 1999; 18: 487-9.

For example, in France , the maximum recommended daily dosage of omega-3 fatty acid is 500 mg/day, for DHA 120 mg / day. Such country specific requirements are taken into account when providing a composition in accordance to the present invention. Hence omega-3-fatty acid amounts deviating from the disclosed amounts but reading on such country specific requirements are equivalently to be considered and are equivalently encompassed by the teachings to this invention.

The supplementation in both EPA /DHA is required , because if the retina contains DHA, EPA is the physiologic precursor of DHA .

The preferred source for omega-3 fatty acid is fish oil. The fish oil content 33% DHA / 23% EPA. The source of the fish oil may have an influence on the content of DHA and EPA. Preferably the subject composition provides approximately 200 mg of an omega-3-fatty acid per tablet, more preferably 200 mg of fish oil, having 33% DHA / 23% EPA.

As used herein, fish oil contains fatty acids esterified by glycerol, and is thus a triglyceride. These fatty acids are classified in 2 groups, namely saturated fatty acids and non-saturated (or unsaturated) fatty acids. Among the non-saturated fatty acid, there are again 2 groups, namely the omega-6 fatty acids and the omega-3 fatty acids.

Sources are :

Natural fish oil , as triglyceride form with approximately 18% EPA and 12% DHA (by weight).

Oil enriched in EPA / DHA (ex : 60 % EPA / 20% DHA)

Oil containing ethyl esters and pure DHA / EPA

Compositions of the present invention may typically contain :

In a per day dosage, a composition may typically contain between 20 and 100 mg (average 66 mg, that is to say 200 mg of oil containing 33% of EPA) and between 10 and 80 mg (average 44 mg, that is to say 200 mg of oil containing 22% of DHA). These 2 fatty acids could be brought in as a triglyceride (fish oil), as an ethyl ester or in pure form.

Preferably the subject composition provides approximately 10 – 600 mg, more preferably 20 – 500 mg, and even more preferably 30 – 400 mg omega-3 fatty acid per day.

BETA-CAROTENE

Beta-carotene, a pro-form of vitamin A, is a lipid-soluble orange pigment found in many vegetables. Beta-carotene is converted to vitamin A in the body with an efficiency of approximately 50 percent. The recommended daily dosage of vitamin A is 5,000 IU corresponding to 3 mg. Beta-carotene has one of the highest antioxidant potentials of the antioxidants.

The rhodopsine, visual pigment necessary for scotopic vision, depends on the Vitamine A physiological amount .

Also, beta carotene as an antioxidant will protect the lutein from oxidation.

It has been reported that there might be an increased risk of fatal coronary heart attacks in men with previous myocardial infarction and an increased risk of lung cancer among male smokers, in particular in individuals who receive 20 mg/day of beta-carotene.

In another aspect, beta-carotene is omitted from the composition of the present invention. Such a composition is preferably recommended for smokers.

When beta-carotene is present, the subject composition preferably provides approximately 2 mg beta-carotene (3334 IU) per tablet.

Each mg beta-carotene corresponds to a potency of 1,667 IU vitamin A.

Should beta- carotene be present in a composition of the present invention, then it would preferably contain approximately 0.5 – 6 mg, more preferably 1 – 4 mg, and even more preferably 2 – 3 mg beta-carotene per day.

Selenium

The DHA supplementation requires supplementation with selenium that plays a protective role on the membranous lipids.

Selenium exhibits also an anti oxidant role as a cofactor for enzymes (such as glutathione peroxidase) that participate directly in the oxidant defense.

Among these enzymes linked with selenium , some would also specifically participate in AMD prevention, namely thioredoxine reductase and selenoprotein P.

The thioredoxine reductase would act in cell rapid increase and in the apoptosis defence.

The selenoprotein P , which represents the blood circulate form of selenium, should protect the endothelial cells of the vessels from oxidative components.

The association vitamine E and selenium is important, because vitamine E is a liposoluble antioxidant, and has a complementary action with respect to the Selenium. Therefore, it must not be omitted as a trace element and is a mandatory ingredient in a composition of the present invention.

As used herein, selenium refers to a selenite salt, such as sodium selenite. Selenium may also be used in the form of selenomethionine or as sodium selenate, or as a mixture thereof. A preferred selenium is sodium selenite.

Preferably the subject composition provides approximately 50 micrograms selenium per tablet.

In a total daily dosage selenium is typically present in an amount of about 15 – 150 micrograms, more preferably from 20 – 100 micrograms and in particular from 30 – 70 micrograms.

In another aspect the present invention pertains to a composition consisting approximately or exactly of from 10 – 150 mg of vitamin C, of from 5 – 30 mg of vitamin E, of from 1 – 20 mg

of lutein, of from 5 – 30 mg zinc, of from 15 – 150 micrograms selenium, of from 5 – 75 micrograms chromium, and of from 10 – 600 mg of an omega-3-fatty acid. Such a precisely defined composition is in particular useful in the manufacture of a medicament to treat and/or prevent, e.g. when given on a daily basis, e.g. in one or in more fractions, e.g. by the oral route or by another systemic route, the ocular pathology known as age related macular degeneration or any other pathological disorder of the retina preferably in a human subject in need of such treatment. Therefore the invention also relates to a method of treating and/or preventing age related macular degeneration or any other pathological disorder of the retina in a subject, comprising administering an effective amount of a composition as defined hereinabove.

The compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

The compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, for example Tween 80 [polyoxyethylene(20)sorbitan mono-oleate; trademark of ICI Americas, Inc, USA].

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Claims

1. A composition comprising:
approximately from 10 – 150 mg of vitamin C,
approximately from 5 – 30 mg of vitamin E,
approximately from 1 – 20 mg of lutein,
approximately from 5 – 30 mg zinc,
approximately from 15 – 150 micrograms selenium,
approximately from 5 – 75 micrograms chromium, and
approximately from 10 – 600 mg of an omega-3-fatty acid.
2. Composition of claim 1, further comprising approximately 0.5 – 6 mg beta-carotene.
3. Composition of claim 1 – 2, wherein said vitamin C is provided as ascorbic acid, sodium ascorbate or as a mixture thereof.
4. Composition of claim 1 - 2, wherein said vitamin E is provided as d,l-alpha tocopheryl acetate.
5. Composition of claim 1 - 2, wherein said omega-3-fatty acid is fish oil with a content of 33% DHA and 23% EPA (weight percent of total amount of fish oil).
6. Composition in accordance to any of the previous claims, wherein the composition comprises:

beta-carotene	2 mg (3344 IU); (+/- 20%)
ascorbic acid	60 mg; (+/- 20%)
vitamin E	10 mg (10 IU); (+/- 20%)
zinc gluconate	15 mg; (+/- 20%)
sodium selenite	50 micrograms; (+/- 20%)
chromium-(III)-trichloride hexahydrate	25 micrograms; (+/- 20%)

lutein (pure Flora Glo)	6 mg; (+/- 20%)
fish oil 33% eicosapentaenoic acid (EPA) : 23% docohexaenoic acid (DHA)	200 mg ; (+/- 20%)

wherein the amounts are weight % of the total weight of said composition.

7. Composition of claim 6, wherein said beta-carotene is omitted.
8. Composition of claim 1 - 7, wherein said zinc is provided as zinc oxide.
9. Composition of any one of claims 1 – 8, wherein said composition is formed into one, two, three or more tablets.
10. Use of a composition in accordance to any of the preceding claims in the preparation of a medicament for the treatment and/or prevention of age related macular degeneration or any other pathological disorder of the retina.
11. Method of treating and/or preventing age related macular degeneration or any other pathological disorder of the retina in a subject, comprising administering an effective amount of a composition in accordance to any one of claims 1 – 9.
12. Method of claim 11, wherein said composition is administered orally.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/375 A61P27/02 A61K31/355 A61K31/047 A61K31/202
A61K33/24 A61K33/30

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)

A61K A61P

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

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

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 649 195 B1 (GORSEK WAYNE F) 18 November 2003 (2003-11-18) column 3	1-12
Y	EP 1 214 893 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 19 June 2002 (2002-06-19) column 21, line 2 - line 3 column 21, line 18 - line 36	1-12
Y	US 2004/001817 A1 (GIAMPAPA VINCENT C) 1 January 2004 (2004-01-01) column 11, paragraph 367 - paragraphs 370,384,385,388 column 12, paragraphs 396,418	1-12
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/

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Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/002303

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TURCOTTE P.: "ANTIOXIDANT VITAMINS, ZINC AND AGE-RELATED MACULAR DEGENERATION: WHAT WE CAN NOW RECOMMEND TO OUR PATIENTS" PRACTICAL OPTOMETRY, vol. 14, no. 1, 2003, pages 35-36, XP001207954 the whole document</p> <p>-----</p>	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/002303

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6649195	B1	18-11-2003	NONE	
EP 1214893	A	19-06-2002	NONE	
US 2004001817	A1	01-01-2004	NONE	