Description

The essential fatty acids (EFAs) are of two types, the n-3 (or omega-3) series derived from alpha-linolenic acid and the n-6 (or omega-6) series derived from linoleic acid. Linoleic acid and alpha-linolenic acid are like vitamins in that they cannot be manufactured in the body and therefore must be provided in the diet. The body can metabolise them along the pathways below and such metabolism is believed to be essential if they are to fulfil their functions. The pathways, sharing it is believed common enzymes, are:

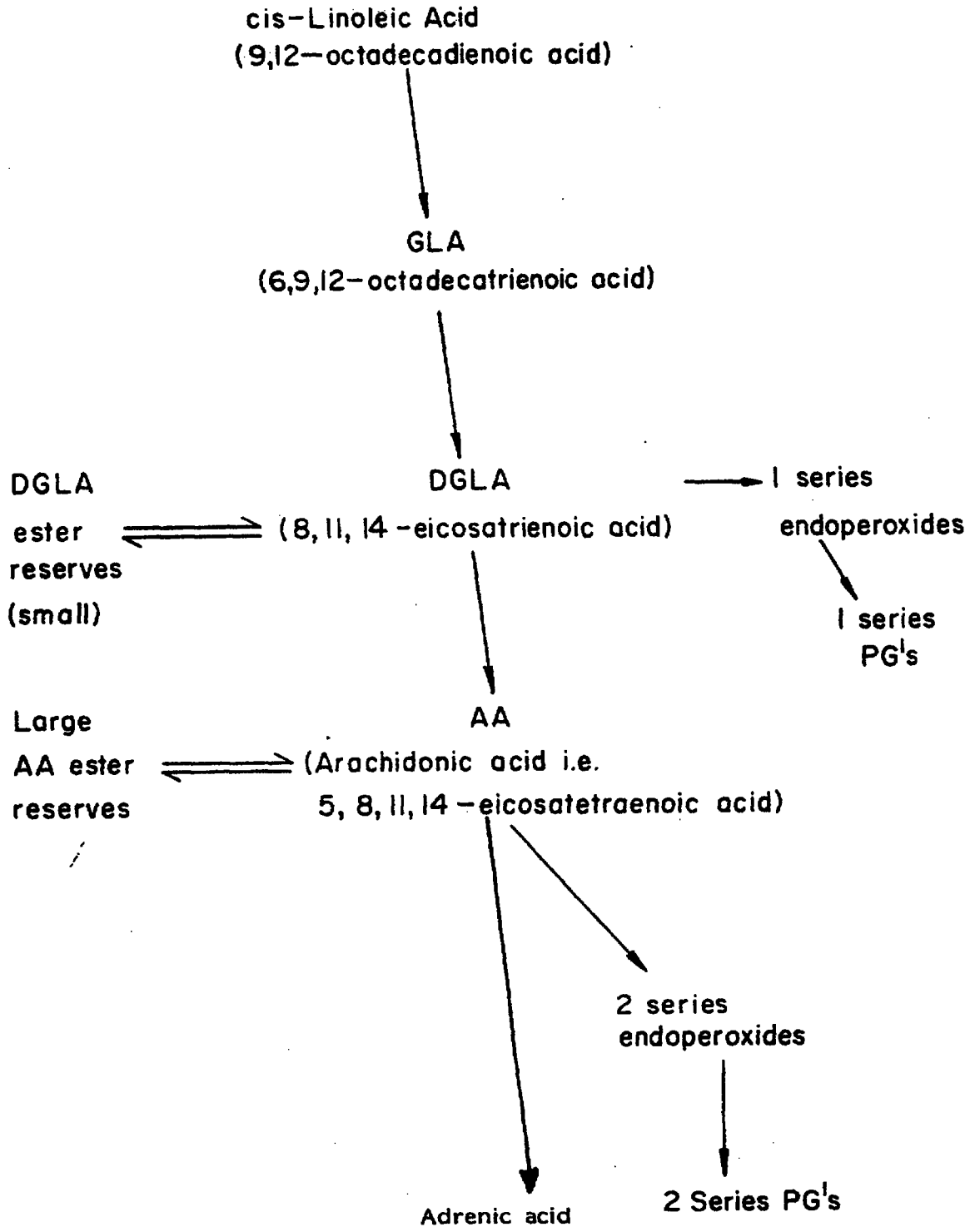
n-6	n-3
18:2 delta-9,12(linoleic acid)	18:3 delta-9,12,15(alpha-linolenic acid)
↓ delta-6 desaturase	↓
18:3 delta-6,9,12(gamma-linolenic acid)	18:4 delta-6,9,12,15
↓ elongation	↓
20:3 delta-8,11,14(dihomo-gamma-linolenic acid)	20:4 delta-8,11,14,17
↓ delta-5 desaturase	↓
20:4 delta-5,8,11,14(arachidonic acid)	20:5 delta-5,8,11,14,17
↓ elongation	↓
22:4 delta-7,10,13,16(adrenic acid)	22:5 delta-7,10,13,16,19
↓ delta-4 desaturase	↓
22:5 delta-4,7,10,13,16	22:6 delta-4,7,10,13,16,19

The pathways are not normally reversible nor, in man, are n-3 and n-6 series acid interconvertible.

The acids, which naturally are of the all-cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g. delta-9,12-octadecadienoic acid or delta-4,7,10,13,16,19-docosahexaenoic acid, but numerical designation such as, correspondingly, 18:2 n-6 or 22:6 n-3 is convenient. Initials, for example, DHA for 22:6 n-3 (docosahexaenoic acid), are also used but do not serve when n-3 and n-6 acids of the same chain length and degree of unsaturation exist. Trivial names in more or less common use in the n-6 series are as shown. Of the n-3 series only 18:3 n-3 has a commonly used trivial name, alpha-linolenic acid. It was characterised earlier than gamma-linolenic acid and reference in the literature simply to linolenic acid, especially in the earlier literature is to the alpha-acid.

In the body, the n-3 acids are metabolised preferentially and as a result, in plasma for example, levels of alpha-linolenic acid (18:3 n-3) are low and 18:4 n-3 and 20:4 n-3 are in trace amounts only. In contrast the n-6 acids are normally present in moderate amounts, though gamma-linolenic acid (GLA) is at low levels, being apparently converted to dihomo-gamma-linolenic acid (DGLA) more rapidly than its relatively slow production from linoleic acid. In both series the elongation stages in the metabolic pathways are much more rapid that the desaturations.

Particular significance of the n-6 series acids lies in prostaglandin (PG) synthesis, the outline of which is believed to be as shown in the following diagram:



The broad outline of this pathway is well known, and it brings out clearly that a major function of essential fatty acids is to act as precursors for 1-series PGs formed from DGLA and 2-series PGs formed from arachidonic acid. Further, it has recently been found that the 22:4 n-6 acid produced from arachidonic acid gives rise to a series of homo-2-series PGs, though their importance is as yet unknown.

DGLA is the key substance. GLA is almost completely and very rapidly converted in the body to DLGA and so for practical purposes the oral administration of DGLA and GLA amounts to the same thing. DGLA can be converted to a storage form or to PGs of the 1-series or, through arachidonic acid, to PGs of the 2-series.

Considering dietary requirements, it is well known, for example, that linoleic acid cannot be made by

the body and so must be taken in the diet. However, it has been generally thought that the body can metabolise linoleic acid to all the other n-6 acids and therefore that provided linoleic acid intake is adequate, no lack of the other n-6 acids will be found.

In previous patent applications (for example Published European Patent Application No. A 0 003 407, U.S. Patent No. 4 273 763; Published European Patent Application No. A 0 004 770, U.S. Patent No. 4 309 415; Published European Patent Application No. 0 019 423, U.S. Patent No. 4 388 324) it has, however, been pointed out that the first enzyme in the pathway, the delta-6 desaturase which, for example, converts linoleic acid to GLA, is not fully effective in a variety of conditions. The administration of GLA or DGLA or both has been suggested 30and has been successful in treating a variety of clinical conditions. Australian Patent No. 524106 relates, inter alia, to the treatment of diabetes mellitus with GLA and/or DGLA and a material, for example, zinc influencing the 1-series/2-series PG balance in the body in favour of 1-series PGs.

In the above patent applications attention is primarily paid to the function of essential fatty acids in prostaglandin metabolism and in particular to their role in securing a proper balance between 1- series and 2-series PGs. Attention is primarily paid therefore to the n-6 acids.

The applicants are, however, becoming increasingly aware of the significance of the essential fatty acids in themselves as set out above. Considerable general interest has been shown in them in recent years, primarily in the acids of the n-6 series both as such and in relation to prostaglandin metabolism, but also in the acids of the n-3 series. The n-6 acids in particular are believed to be required in the body for the structure of membranes in and around cells, maintaining normal flexibility, fluidity and permeability of such membranes and the n-3 acids are unlikely to have a merely passive role.

Diabetes mellitus is a common condition in which there is either a deficiency of insulin or a resistance to the action of insulin. This produces severe abnormalities in metabolism, especially of carbohydrates. These abnormalities can lead to coma and death. The disease can be treated by insulin or in milder cases by diet and oral drugs. However, while these measures are relatively successful in correcting the acute problems of carbohydrate metabolism, it is increasingly recognised that the survivors in the long term suffer a range of damage to large and small blood vessels, to the eyes, kidneys and nerves. The nerve damage, known as diabetic neuropathy, leads to a range of abnormalities. The reasons for these long term complications are not understood but the applicants believe they lie at least in part in diabetics being unable to perform the normal reaction of the delta-6 desaturase. On this basis diabetics may be expected to benefit from the administration of GLA or one of its further metabolites and/or of 18:4 n-3 or one of its further metabolites, so by-passing the defective step. The applicants have found that the administration of GLA is indeed beneficial to diabetics suffering from diabetic neuropathy.

An improvement in methods for measuring the function of the nerves in humans is discussed in G.A. Jamal et al, "An Improved Automated Method for the Measurement of Thermal Thresholds", J. Neurol Neurosurg Psych 48: 354-60 (1985). Using this test, many diabetics show defective nerve function. A group of 16 diabetics with such defective nerve function has been studied and its members have been treated for three months with either evening primrose oil containing GLA, or a placebo containing no GLA. After three months the group treated with evening primrose oil showed a highly significant improvement in peripheral nerve function as compared with the placebo group. The GLA appears to reverse already established abnormalities in diabetics, and it is also to be expected to be effective in preventing development of such abnormalities.

It is also anticipated that the further metabolites of GLA will improve diabetic neuropathy in diabetic patients, and since the postulated delta-6 desaturase abnormality will also affect the n-3 acids, it is to be expected that 18:4 n-3 and its higher metabolites will contribute to or enhance the therapeutic and preventative effects of GLA and indeed have benefit alone.

The success of GLA in the treatment of diabetic neuropathy strongly suggests that it is also likely to be of value in the prevention and treatment of other long term complications of diabetes, including those in the cardiovascular system, the kidneys and the eyes.

In the light of the discussion above the present invention may be summarised as:

For the preparation of a medicament for prevention or treatment of diabetic neuropathy and the other long term complications of diabetes mellitus including complications in the cardiovascular system, kidneys and eyes, the use, alone or in an acceptable pharmaceutical carrier or diluent, of one or both of (i) gamma-linolenic acid and/or one or more of the metabolites of gamma-linolenic acid (DGLA, AA, 22:4 n-6 or 22:5 n-6) and (ii) 18:4 n-3 and/or one or more of the metabolites of 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto.

All the acids may be administered in the form of the acid itself or as an ester, amide, salt or any other functional derivative capable of being converted to the acid within the body and may be from natural or

synthetic sources. Conversion of derivatives, of which glyceride esters such as those of GLA in evening primrose oil are the preferred form, is shown by their having the desirable effect in the body of the acids themselves or directly by analysis of plasma or other tissue by standard techniques, for example those of Pelick et al, page 23, "Analysis of Lipids and Lipoproteins" Ed. Perkins, American Oil Chemists Society, Champaign, Illinois, U.S.A.

Doses for each acid are from 1 mg to 100 g per unit dose, preferably 50 mg to 5 g per unit dose, conveniently in conventional gelatine capsules.

If it is not desired to have compositions comprising the different active materials together, packs may be prepared comprising the materials presented for separate, or part joint and part separate administration in the appropriate relative amounts, and use of such packs is within the purview of this invention.

Conveniently physiologically equivalent derivatives of gamma-linolenic acid and dihomo-gamma-linolenic acid for use according to the invention, as with the other acids, include salts, amides, esters including glyceride esters and alkyl (e.g. C_1 to C_4) esters, and phospholipids. As noted above, reference to the acids in the claims and elsewhere herein are to be taken as including them when in the form of said derivatives.

If desired, pharmaceutical compositions may be produced for use in the invention by associating the natural or synthetic acids, as such or as derivatives, with an acceptable pharmaceutical vehicle. It is, however, at present convenient to incorporate at least the gamma-linolenic acid into compositions in the form of an available oil having a high gamma-linolenic acid content, hence reference to "oil" herein.

At the present time known natural sources of oils having a high gamma-linolenic acid content are few (there are no known natural sources of significant amounts of dihomo-gamma-linolenic acid). One source of oils currently available is the seed of evening primrose species such as Oenothera biennis L. and Oenothera lamarckiana, the oil extract therefrom containing gamma-linolenic acid (about 8%) and linoleic acid (about 72%) in the form of their glycerides together with other glycerides (percentages based on total fatty acids). Other sources of gamma-linolenic acid are Borage species such as Borago officinalis which, though current yield per acre is low, provide a richer source of gamma-linolenic acid then Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The oil is extracted from the seed by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

Fractination of a typical sample of this oil in the form of methyl esters shows the relative proportions:

Palmitate	6.15
Stearate	1.6
Oleate	10.15
Linoleate	72.6
Gamma-linolenate	8.9

The seed oil extracts referred to above can be used as such or can, for example, if desired, be fractionated to yield an oily composition containing the triglycerides of gamma-linolenic and linoleic as the main fatty acid components, the gamma-linolenic acid content being if desired a major proportion. Seed oil extracts appear to have a stabilising effect upon dihomo-gamma-linolenic acid if present.

Natural sources of 22:4 and 22:5 n-6 acids include adrenal glands (22:5) and kidneys (22:4) obtained from slaughter houses, and 22:4 in the fat of the American Snapping Turtle. The n-3 acids are available from fish oils, particularly 20:5 n-3 and 22:6 n-3.

The acids can be isolated from these sources by, for example, saponification under mild non-oxidising conditions followed by preparative gas liquid chromatography. Synthesis of the acids is difficult but not impossible and provides another source.

Advantageously, a preservative is incorporated into the preparations: alpha-tocopherol in concentration of about 0.1% by weight has been found suitable for the purpose.

The invention is chiefly described in terms of use of pharmaceutical compositions, but it will be understood that the gamma-linolenic and other acids being in the nature of dietary supplements, could be incorporated in a dietary margarine or other foodstuffs: use of such foodstuffs, possibly containing other active materials and generally referred to in this description as dietary or pharmaceutical compositions, are within the purview of the invention and thus of the term pharmaceutical compositions or the like used in the claims.

It will be understood that where a disorder of a kind calling for treatment in animals arises, the invention while described primarily in terms of human medicine and treatment is equally applicable in the veterinary

field.

The compositions used according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1 082 624 and in any case very well known generally for any particular kind of preparation. Thus for example, tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid.

Advantageously a preservative is incorporated into the preparations. Alpha-tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following are specific Examples of the invention against the symptoms of diabetic neuropathy.

EXAMPLE 1

A capsule containing 0.3 g evening primrose oil and 0.2 g mackerel oil administered six times per day.

EXAMPLE 2

A capsule containing 0.35 g evening primrose oil and 0.15 g salmon oil administered eight times per day.

EXAMPLE 3

A 0.25 g capsule containing 150 mg of GLA and 100 mg of 20:5 n-3 administered three times per day.

EXAMPLE 4

A capsule containing 50 mg of DGLA, 50 mg of AA, 20 mg of 22:4 n-6, 20 mg of 22:5 n-6, 50 mg of 20:5 n-3, 20 mg of 22:5 n-3 and 20 mg of 22:6 n-3 taken four times a day.

EXAMPLE 5

A capsule containing 0.5 g evening primrose oil administered six times per day.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. For the preparation of a medicament for prevention or treatment of diabetic neuropathy and the other long term complications of diabetes mellitus including complications in the cardiovascular system, kidneys and eyes, the use, alone or in an acceptable pharmaceutical carrier or diluent, of one or both of (i) gamma-linolenic acid and/or one or more of the metabolites of gamma-linolenic acid (DGLA, AA, 22:4 n-6 or 22:5 n-6) and (ii) 18:4 n-3 and/or one or more of the metabolites of 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3), as such or in the form of an ester salt, amide or other derivative convertible in the body thereto.

2. The use as claimed in claim 1 characterised in that the amounts of each said acid are 1 mg to 100 g, or sub-multiples thereof, per unit dose.

3. The use as claimed in claim 1 characterised in that the amounts of each said acid are 50 mg to 5 g per unit dose.

Claims for the following Contracting States : AT, ES, GR

1. Method for the preparation of a medicament for prevention or treatment of diabetic neuropathy and the

field.

The compositions used according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1 082 624 and in any case very well known generally for any particular kind of preparation. Thus for example, tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid.

Advantageously a preservative is incorporated into the preparations. Alpha-tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

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EXAMPLE 4

A capsule containing 50 mg of DGLA, 50 mg of AA, 20 mg of 22:4 n-6, 20 mg of 22:5 n-6, 50 mg of 20:5 n-3, 20 mg of 22:5 n-3 and 20 mg of 22:6 n-3 taken four times a day.

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Claims

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1. For the preparation of a medicament for prevention or treatment of diabetic neuropathy and the other long term complications of diabetes mellitus including complications in the cardiovascular system, kidneys and eyes, the use, alone or in an acceptable pharmaceutical carrier or diluent, of one or both of (i) gamma-linolenic acid and/or one or more of the metabolites of gamma-linolenic acid (DGLA, AA, 22:4 n-6 or 22:5 n-6) and (ii) 18:4 n-3 and/or one or more of the metabolites of 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3), as such or in the form of an ester salt, amide or other derivative convertible in the body thereto.

2. The use as claimed in claim 1 characterised in that the amounts of each said acid are 1 mg to 100 g, or sub-multiples thereof, per unit dose.

3. The use as claimed in claim 1 characterised in that the amounts of each said acid are 50 mg to 5 g per unit dose.

Claims for the following Contracting States : AT, ES, GR

1. Method for the preparation of a medicament for prevention or treatment of diabetic neuropathy and the

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other long term complications of diabetes mellitus including complications in the cardiovascular system, kidneys and eyes, comprising the mixing of an acceptable pharmaceutical carrier or diluent, with one or both of (i) gamma-linolenic acid and/or one or more of the metabolites of gamma-linolenic acid (DGLA, AA, 22:4 n-6 or 22:5 n-6) and (ii) 18:4 n-3 and/or one or more of the metabolites of 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto.

2. The method as claimed in claim 1 characterised in that the amount of each said acid are 1 mg to 100 g, or sub-multiples thereof, per unit dose.

3. The method as claimed in claim 1 characterised in that the amounts of each said acid are 50 mg to 5 g per unit dose.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Für die Zubereitung eines Medikamentes zur Vorbeugung oder Behandlung von diabetischer Neuropathie und anderen langfristigen Komplikationen von Diabetes Mellitus einschließlich Komplikationen in dem Herzgefäßsystem, Nieren und Augen, die Verwendung, allein oder in einer akzeptablen, pharmazeutischen Trägersubstanz oder Verdünnungsmittel, einer oder beide (i) Gamma-Linolen-säure und/oder eines oder mehrerer der Metabolite der Gamma-Linolensäure (DGLA, AA, 22 : 4 n-6 oder 22 : 5 n-6) und (ii) 18 : 4 n-3 und/oder eines oder mehrerer der Metaboliten der 18 : 4 n-3 (20 : 4 n-3, 20 : 5 n-3, 22 : 5n-3, 22 : 6 n-3), als solche oder in der Form eines Estersalzes, Amides oder anderen Derivates, das sich im Körper dazu umwandelt.

2. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Mengen jeder besagten Säure 1 mg bis 100 g oder Submultiple davon je Einheitsdosis betragen.

3. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Mengen jeder besagten Säure 50 mg bis 5 g je Einheitsdosis betragen.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren für die Zubereitung eines Medikamentes zur Vorbeugung oder Behandlung von diabetischer Neuropathie und den anderen langfristigen Komplikationen von Diabetes-Mellitus einschl. Komplikationen in dem Herzgefäßsystem, Nieren und Augen, das das Mischen einer akzeptablen pharmazeutischen Trägersubstanz oder Lösungsmittel mit einer oder beiden (i) Gamma-Linolensäure und/oder eines oder mehrerer der Metaboliten von Gamma-Linolensäure (DGLA, AA, 22 : 4 n-6 oder 22 : 5 n-6) und (ii) 18 : 4 n-3 und/oder eines oder mehrerer der Metaboliten von 18 : 4 n-3 (20 : 4 n-3, 20 : 5 n-3, 22 : 5 n-3, 22 : 6 n-3), als solche oder in der Form eines Esters, Salzes, Amides oder anderen Derivates, das im Körper dazu umwandelbar ist, umfaßt.

2. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß die Menge jeder besagten Säure 1 mg bis 100 g oder Submultiple davon je Einheitsdosis beträgt.

3. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß die Mengen jeder besagten Säure 50 mg bis 5 g je Einheitsdosis betragen.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pour la préparation d'un médicament pour la prévention ou le traitement de la neuropathie diabétique et des autres complications de longue durée du diabetes mellitus, comprenant les complications dans le système cardio-vasculaire, les reins et les yeux, l'utilisation, seule ou dans un support ou diluant pharmaceutiquement acceptable, de l'un ou des deux parmi :
   (i) l'acide gamma-linolénique et/ou un ou plusieurs des métabolites de l'acide gamma-linolénique (DGLA, AA, 22:4 n-6 ou 22:5 n-6) ; et
   (ii) 18:4 n-3 et/ou un ou plusieurs des métabolites de 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-

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3),

en tant que tels ou sous la forme d'un ester, d'un sel, d'un amide ou d'un autre dérivé convertible en ceux-ci dans le corps.

2. Utilisation selon la revendication 1, caractérisée par le fait que la quantité de chacun desdits acides est de 1 mg à 100 g, ou un sous-multiple de celle-ci, par dose unitaire.

3. Utilisation selon la revendication 1, caractérisée par le fait que la quantité de chacun desdits acides est de 50 mg à 5 g par dose unitaire.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé pour la préparation d'un médicament pour la prévention ou le traitement de la neuropathie diabétique et des autres complications de longue durée du diabetes mellitus, comprenant les complications dans le système cardio-vasculaire, les reins et les yeux, ledit procédé comprenant le mélangeage d'un support ou diluant pharmaceutiquement acceptable avec l'un ou les deux parmi :

   (i) l'acide gamma-linolénique et/ou un ou plusieurs des métabolites de l'acide gamma-linolénique (DGLA, AA, 22:4 n-6 ou 22:5 n-6) ; et

   (ii) 18:4 n-3 et/ou un ou plusieurs des métabolites de 18:4 n-3 (20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3),

   en tant que tels ou sous la forme d'un ester, d'un sel, d'un amide ou d'un autre dérivé convertible en ceux-ci dans le corps.

2. Procédé selon la revendication 1, caractérisé par le fait que la quantité de chacun desdits acides est de 1 mg à 100 g, ou un sous-multiple de celle-ci, par dose unitaire.

3. Procédé selon la revendication 1, caractérisé par le fait que la quantité de chacun desdits acides est de 50 mg à 5 g par dose unitaire.