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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITION COMPRISING FOLIC ACID AND CARNITINE USEFUL TO ENHANCE MALE FERTILITY

(57) Abstract: Composition and use thereof for enhancing male fertility.
COMPOSITION COMPRISING FOLIC ACID AND CARNITINE USEFUL TO ENHANCE MALE FERTILITY

The present invention relates to compositions comprising folic acid and carnitine and to uses thereof.

In the industrialized countries, increasingly, the deterioration of male fertility is observed. Changed nutritional habits, stress, smoking, traces of man-made polluting chemical with estrogen-like physiological effects and the like have been suspected being a likely cause of that.

Ever since, the influence of nutritional factors amongst others has been gained ever increasing attention to counteract this development. EP-B1-1039 894 devises a mixture of L-carnitine and Acetyl-L-carnitine for increasing male sperm quality. However, the amount of that composition intended for human administration is in the range of several grams of substance; apart from cost considerations for human consumers, such amounts may cause symptoms of diarrhoea if taken in amounts of >3 g a day.

It is an object of the present invention to devise another nutritional composition improving the fertility of a human male. Another object is the use of such composition for improving male fertility.

This object is solved by a composition according to claim 1 and a use thereof according to claim XXX. The composition comprises Carnitine or an Acyl-Carnitine or a salt thereof and folic acid or a salt thereof. Folic acid, or folate, is known to be a carrier of C1-units in the organism. Folic acid is also known under the non-systematic name of pteroylglutamic acid (PGA). Under folic acid in the context of the present invention, any known active metabolic equivalent of folic acid is to be understood, e.g. folate, tetrahydrofolate, 5-methyl-tetrahydrofolate, 5,10-methylentetrahydrofolate, 10-formyltetrahydrofolate. More preferably, the folic acid is 5-methyl-tetrahydrofolate, 5,10-methylentetrahydrofolate or salts thereof. Most preferably, the folic acid is 5-methyl-tetrahydrofolate. The methylated form of folic acid (including its salts which dissolve in the gastrointestinal tract) is the form actually absorbed most optimally in the intestine amongst all C1-modified forms of folic
acid; non-methylated folic acid is converted to the methyl form for transport across the intestinal barrier by specialized enzyme systems.

Preferably, such folic acid is man-made and is not comprised as a natural compound of food stuff. Due to this, the folic acid content of the present composition is most efficiently absorbed in the guts. – Foods deliver folate mostly in the ‘bound’ form, that is, combined with a string of amino acids, predominantly glutamate, therefore termed ‘polyglutamate’. The intestine prefers to absorb the free folate form, prejudice to the above said on specific methylation systems for efficient transport. Due to this, nutritionists calculate the folic acid contents of diets in dietary folate equivalents (DFE): Synthetic folate is considered to be 1.7 more potent (1.7 DFE) upon ingestion than naturally comprised dietary ‘folate’.

Carnitine according to the present invention may be (DL)-Carnitine or, preferably, essentially pure L-Carnitine. Such Carnitine may as well be Acyl-Carnitine, in particular 2-Acetyl-Carnitine. Such Carnitine may be employed either as an inner salt or as a simple or complex salt together with other ionic substances such as, but not limited to, chloride, fumarate, tartrate, citrate, isocitrate, (−)-hydroxycitrate, magnesium, calcium, cholin, either alone or in suitable combinations, particularly as non-hygroscopic complex salts, e.g. L-Carnitine-magnesium-citrate, L-Carnitine-magnesium-hydroxycitrate or L-Carnitine-cholin-tartrate. In even more preferred embodiments, Carnitine according to the present invention is either L-Carnitine-tartrate, L-Carnitine-magnesium-citrate or L-Carnitine-magnesium-(−)-hydroxycitrate. Carnitine is, in its L-form, a naturally occurring substance involved in energy metabolism in mitochondria that is widely used as a nutritional supplement, e.g. for slimming and is a well-known substance without adverse effects.

Surprisingly, upon oral administration to a human, the composition of the present invention displays a synergistic, male fertility enhancing effect. Sperm count and density of sperm cells with normal, non-pathologic morphology are synergistically enhanced. In addition, L-carnitine contributes to sperm motility. Sperm count and density can be determined using standard microscopic techniques (Adelmann, M. eta l., Atlas of sperm cell morphology, Chicago, ASCP Press, 1989; Schover, L. et al., Overcoming Male Infertility, New York, Wiley, 2000). Preferably, sperm count is determined according to the method of Overstreet,
dysfunction, New York, Springer-Verlag, p.39 ff). Whereas sperm concentration relates to
the number of sperm that is found in each milliliter of semen, the sperm count — total
sperm count — is the total number of sperm present in the semen (semen volume multiplied
by sperm concentration). This value accurately describes the sperm production by the
testicles. Briefly, appropriate dilutions of semen (1:10 or 1:20 using water were applied to
a Neubauer hemacytometer (Fisher, Pittsburgh, PA), allowed to settle and counted. From
this count, density (10^6 sperm/mL) was determined, and total count was calculated by
multiplying the density by the measured ejaculate volume.

For male individuals considered healthy, the normal value for sperm concentration is
approx. ≥ 20 million/ml. The normal total sperm count is ≥ 40 million. The composition
and its use, respectively, according to the present invention, is most effective in individuals
having abnormally lowered values of sperm count and density as compared to these
standard values.

Preferably, the male person to whom the composition according to the present invention is
administered has a daily intake of folic acid, calculated as DFE, that is below the
recommended 400 μg/day of folic acid according the RDA guidelines (RDA:
Recommended daily allowance; US health services). The blood plasma total folate
concentration should thus be below a threshold of about 7nmol/L as is easily determined by
commercial radio immunoassay (Quantaphase B-12 folate Radioassay; BioRad, Hercules,
CA). It should be noted that folate is comprised mostly in fresh vegetables or certain fruits,
but is very poorly present e.g. in milk products. Furthermore, storage/processing of foods,
and in particular cooking of food, very efficiently destroys folic acid in foodstuffs. Only
raw, fresh vegetables or freshly prepared orange juice do provide sufficient amounts of
folic acid if taken in effective amounts.

Preferably, the male person to whom the composition according to the present invention
is administered is deficient in folic acid for other reasons than insufficient nutritional
intake. Deficiency in this context does not relate to lowered total levels of folate e.g. in
blood plasma. Quite in contrast, the blood plasma levels in such individuals are not
significantly lowered as compared to healthy, balancedly fed individuals. Rather, the metabolic balance of biochemically active methyl- and non-methyl derivatives of tetrahydrofolate acid is shifted. The deficiency consists in lowered amount of non-methyl tetrahydrofolate acid. For instance, it has been observed that medicaments, e.g. such often taken substances such as gastric antiacidants or aspirin (acetyl-salicylic acid) and common acitivities such as smoking or consumption of alcoholic beverages interfered with normal folic acid metabolism, lowering the effective amounts of non-methyl tetrahydrofolate acid vs. methylated tetrahydrofolate acid (5-methyl tetrahydrofolate acid) in vivo. Low seminal plasma concentration of non-methylated-folate has been found to correlate with inferior sperm count and density (Wallock, L. et al, 2001, Low seminal plasma folate concentrations are associated with low sperm density and count in male smokers and non-smokers, Fertility and sterility, 75, 2:252-259). Also, fairly common congenital reasons for such subtle in vivo folate deficiencies exist: A common genetic polymorphism (C677T) of 5,10-
methylenetetrahydrofolate reductase (EC 1.5.1.20) exists, homozygous individuals having lowered levels of methionine when folate status is compromised (Ma, J. et al., 1996, Methyltetrahydrofolate reductase polymorphisms, plasma folate, homocysteine, and risk of myocardial infarction in US physicians, Circulation 1996, 94:2410-2416 and references cited therein). According to the present invention, a male-fertility affecting deficiency in non-methyl tetrahydrofolate acid or its corresponding salt is determined by measuring the concentration of folates in seminal plasma (according to the method of Tamura, T., Microbiological assays of folates. In: Picianno, M.F. et al., Folic acid metabolism in health and disease, New York, Wiley-Liss, 1990: 121-137). Employing two different strains of microorganisms, the value for total and non-methyl tetrahydrofolate acid can be determined. A proportion of less than 40%, more preferably of less than 35%, and most preferably of less than 30 % of the non-methyl tetrahydrofolate acid in total seminal plasma folat (which may be in the range of approx. 5-25 nmol/L folat, more commonly in the range of 10-20 nmol/L folat) is indicative of a deficiency in non-methyl tetrahydrofolate acid according to the present invention.

Whereas lowered folate intake or disbalanced folate metabolism is crucial for maximum effectiveness of using the composition of the present invention for enhancing male fertility, the person administered the present composition does not need to be abnormally deficient
in carnitine. L-carnitine can be taken over a wide range of dosage with ever improving
effect up to the range of several grams.

A further beneficial side effect of carnitine administration is the reduction of serum
cholesterol levels based on metabolic effects (Cacciatore, L. et al., (1991), Drugs Exp.
Clin. Res. 18, 355 ff.). This further promotes a patient's health. Folic acid itself is an
essential vitamin needed for anabolic activities (nucleotide synthesis, aminoacid synthesis)
in the body.

Preferably, the composition in accordance with the present invention comprises at least 5
mg up to 8000 mg carnitine per 100 µg of folic acid inhibitor, more preferably 100 to 2000
mg carnitine per 100 µg of folic acid, most preferably 250 to 850 mg carnitine per 100 µg
of folic acid.

According to the present invention, the folic acid may amount to between 10 to 1000 µg,
preferably between 40 to 400µg in suitable oral dosage forms comprising the composition
of the present invention. For example, a daily dose for folic acid supplementing the diet can
be 50-300 µg for an average adult and is achieved by multiple oral intake of a capsule or
tablet. Carnitine may amount to between 50 to 8000 mg in suitable oral dosage forms of the
composition. Preferably, it amounts to in between 250 to 1000 mg for the purpose of
enhancing the male fertility.

Preferably, the composition of the present invention should be administered for at least 2-4
weeks prior to detecting the effect on sperm quality as described above. The present
invention should essentially work in mammalian males of all species, preferably it works in
humans. More preferably, said human males are older than 30 years of age. At this age,
folic acid metabolism is more easily disturbed and a deficiency in non-methyl tetrafolic
acid provoked than in younger human males.

The composition according to the present invention may be added to foodstuff, i.e. the diet,
or swallowed as a freshly prepared suspension. For example, the composition may be
added to low-calorific cereal or chocolate bars or similar snacks comprising a certain
amount of fat. Dispersible powders and granules comprising the composition according to
the present invention are a preferred embodiment. Such powders or granules may be
suitable for preparation of an aqueous suspension by the addition of water and may provide
the active ingredient in admixture with a dispersing or wetting agent, a suspending agent,
and one or more preservatives. Preferably, the composition is prepared as an oral dosage
form and may comprises further, pharmaceutically acceptable excipients.

Such excipients include inert diluents such as calcium carbonate, sodium carbonate,
lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents,
such as corn starch and alginic acid; binding agents such as starch, gelatin or acacia; and
lubricating agents such as magnesium stearate, stearic acid or talc. Tablets may be uncoated
or may be coated with known techniques to delay disintegration and absorption in the
gastrointestinal tract and thereby provide a sustained action over a longer period of time.
For example, a time delay material such as glycercyl monostearate or glycercyl stearate alone
or with a wax may be employed.

In another preferred embodiment, oral dosage forms such as tablets, capsules or
microbeads are coated with an enteric coating which prevents dissolution in the acidic
environment of the stomach. Instead, this coating dissolves in the small intestine at a more
neutral pH. Complex organic molecules such as lipase inhibitors, in particular lipstatin, are
susceptible in varying degrees to acid hydrolysis. Such enteric coated compositions are
described by Bauer et al. (Coated Pharmaceutical Dosage Forms: Fundamentals,
Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials,

Formulations for oral use may also be presented as hard gelatin capsules wherein the active
ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium
phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with
water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Oil suspensions may be formulated by suspending the active ingredients in a vegetable oil,
such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid
paraffin. The oil suspension may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agent, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by an added antioxidant such as ascorbic acid.

Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. It is also possible to add further slimming agents such as glycosidase inhibitors, e.g. acarbose, whose function is to hinder breakdown of carbohydrates such as starch in the intestine. This further reduces the calorific value of the diet.

In another preferred embodiment, the composition of the present invention further comprises one or several vitamins such as e.g. Vitamin A, Vitamin D or Vitamin E. Such composition may further comprise essential fatty acids such as linolic acid, linolenic acid or omega-3 polyunsaturated fatty acids.

It is a further object of the present invention to provide a method to using the composition of the present invention to enhance male fertility, i.e. to increase sperm count and density. All of the above said applies to this further object of the present invention alike, alone or in suitable combination.

It is possible to achieve said fertility enhancing effect not only by ingesting compositions combining carnitine and folic acid as described above, but as well by injecting pharmaceutical preparations of folic acid concomitant with oral ingestion of carnitine or by ingesting stepwise separately prepared formulations of carnitine and folic acid, respectively. It is also possible to saturate the body’s need for carnitine once a day by a certain dose of carnitine, effective amounts being described above, whilst ingesting folic acid repeatedly concomitant with the ingestion of diet, or vice versa. However, it is equally possible to employ retard-capsules or -tablets which continuously release the carnitine over a prolonged period of time.

It is also possible to prepare dosage forms combining, according to the present invention, folic acid and Carnitine whilst not bringing them physically in admixture. Such
pharmaceutical dosage forms might be e.g. gelatine capsules having a partitioning wall or double walled capsules consisting essentially of two separate capsules one being inserted into the other.

5 Dosage forms combining carnitine and folic acid, separately as said before or in physical admixture, are a further object of the present invention. Even more generally, a produce comprising folic acid and carnitine or an Acyl-carnitine or a salt thereof as a combinatorial medicine kit for simultaneous, separate or temporally staggered application is an object of the present invention. Such items a generally termed kits-of-parts and may e.g. consist of separate blister bags comprised in a single package.

Example 1

Composition and pharmaceutical dosage form comprising Carnitine (commercial L-Carnitine, Lonza Ltd.) and folic acid.

A hard gelatine capsule is filled with approx. 447 mg of a powder mixture. The particle size is <0.8 μm. The powder has been mixed by addition of the fine-milled, solid compounds in a conventional kneading machine. The composition of the powder mixture is given below:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Carnitine (Carnitine-Mg-Citrate, Lonza Ltd.)</td>
<td>300 mg</td>
</tr>
<tr>
<td>folic acid</td>
<td>400 µg of folic acid</td>
</tr>
<tr>
<td>Sodium-stearate</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>60</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>2 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>37 mg</td>
</tr>
<tr>
<td>Talcum</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Sodium-Carboxymethyl-starch</td>
<td>8.5 mg</td>
</tr>
<tr>
<td>Polyvinylpolypyrrolidom</td>
<td>8.5 mg</td>
</tr>
<tr>
<td>Acarbose</td>
<td>25.0 mg</td>
</tr>
</tbody>
</table>
Claims

1. Composition comprising folic acid or a salt thereof and carnitine or an acyl-carnitine or a salt thereof.

2. Composition according to claim 1, characterised in that the composition further comprises a pharmaceutically acceptable excipient.

3. Composition according to one of the preceding claims, characterised in that the ratio of Carnitine to folic acid is 10 to 8000 mg L-Carnitine per 100 µg of folic acid.

4. Produce comprising folic acid and carnitine or an Acyl-carnitine or a salt thereof as a combinatorial medicine for simultaneous, separate or temporally staggered application.

5. Oral dosage form comprising a composition according to claim 1.

6. Dosage form according to claim 5, characterised in that it is a tablet or a capsule.

7. Use of a composition according to claim 1 or a produce according to claim 4 for enhancing male fertility.

8. Use of a composition according to claim 1 or a produce according to claim 4 for enhancing sperm count or density in a mammalian, preferably human, male.

9. Use of a composition according to claim 1 or a produce according to claim 4 for enhancing sperm count and density in a mammalian, preferably human, male.

10. Method for enhancing the fertility of a human male wherein an effective, sperm count and density enhancing amount of a composition comprising folic acid and a carnitine or acyl-carnitine, or salts thereof, is administered to said male.
### A. CLASSIFICATION OF SUBJECT MATTER

**IPC** 7 A61K31/505 A61K31/205

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)

**IPC** 7 A61K

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, PAJ, EMBASE, BIOSIS

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 00 53176 A (MELEGARI PIERANGELO ;INTROINI CARLO (IT); UNI CI S R L (IT); BORGO) 14 September 2000 (2000-09-14) claims 4,7,43</td>
<td>1-10</td>
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<tr>
<td>Y</td>
<td>EP 0 539 336 A (SIGMA TAU IND FARMACEUTI) 28 April 1993 (1993-04-28) claims 1-5</td>
<td>1-10</td>
</tr>
<tr>
<td>Y</td>
<td>US 6 235 784 B1 (CAVAZZA CLAUDIO) 22 May 2001 (2001-05-22) column 2, line 64 -column 3, line 4 column 4, line 52 - line 56</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C. Patent family members are listed in 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
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- **"T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- **"C"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- **"X"** 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.

- **"X"** document member of the same patent family

**Date of the actual completion of the international search:** 5 February 2003  
**Date of mailing of the international search report:** 27/02/2003

**Name and mailing address of the ISA:**
European Patent Office, P.B. 5618 Patentlaan 2 NL – 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016

**Authorized officer:** Loher, F
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<tr>
<td>Y</td>
<td>BENTIVOGLO GIORGIO ET AL: &quot;Folinic acid in the treatment of human male infertility.&quot; FERTILITY AND STERILITY, vol. 60, no. 4, 1993, pages 698-701, XP009005286 page 699, right-hand column, paragraph 4 -page 700, left-hand column, paragraph 2</td>
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<td>Y</td>
<td>WALLOCK LYNN M ET AL: &quot;Low seminal plasma folate concentrations are associated with low sperm density and count in male smokers and nonsmokers.&quot; FERTILITY AND STERILITY, vol. 75, no. 2, February 2001 (2001-02), pages 252-259, XP002230097 page 252, left-hand column, paragraph 2 page 258, right-hand column, paragraph 2 page 258, right-hand column, last paragraph -page 259, left-hand column, paragraph 1</td>
<td>1-10</td>
</tr>
<tr>
<td>X</td>
<td>US 5 904 924 A (GAYNOR MITCHELL L ET AL) 18 May 1999 (1999-05-18) column 4, line 51; claim 1 column 5, line 12</td>
<td>1-5</td>
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<tr>
<td>X</td>
<td>WO 98 33494 A (KOSLAB JOHN V) 6 August 1998 (1998-08-06) page 50; table 4</td>
<td>1-6</td>
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</table>
Continuation of Box I.1

Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

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Continuation of Box I.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy
## Box I  Observations where certain claims were found unsearchable (Continuation of item 1 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. **X** Claims Nos.:  
   - because they relate to subject matter not required to be searched by this Authority, namely:  
     
     see FURTHER INFORMATION sheet PCT/ISA/210

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 II  Observations where unity of invention is lacking (Continuation of item 2 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.
<table>
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