(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 May 2006 (18.05.2006)

PCT

(10) International Publication Number
WO 2006/050794 A1

(51) International Patent Classification:
A61K 31/205 (2006.01) *A61K 31/191* (2006.01)
A61K 31/519 (2006.01) *A61K 31/4155* (2006.01)
A61K 31/4418 (2006.01) *A61P 15/10* (2006.01)

(21) International Application Number:
PCT/EP2005/011238

(22) International Filing Date: 19 October 2005 (19.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
RM2004A000561
11 November 2004 (11.11.2004) IT

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

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:** USE OF ACETYL L-CARNITINE IN COMBINATION WITH PROPIONYL L-CARNITINE AND SILDENAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION

(57) **Abstract:** The use of acetyl L-carnitine in combination with propionyl L-carnitine and sildenafil is described for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction secondary to all those conditions in which there is distress or iatrogenic damage of the lesser pelvis within which the neurovascular bundles of the penis run.

WO 2006/050794 A1

"Use of acetyl L-carnitine in combination with propionyl L-carnitine and sildenafil for the treatment of erectile dysfunction"

The present invention relates to the use of acetyl L-carnitine and sildenafil for the preparation of a medicament for the treatment of erectile dysfunction (ED) secondary to all those conditions in which there is distress or iatrogenic damage or trauma of the lesser pelvis within which the neurovascular bundles of the penis run.

Damage to the lesser pelvis within which the neurovascular bundles of the penis run can be caused, for example, by radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles, by bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp); by prostate irradiation for cancer; or by rectal surgery.

The percentage of patients with erectile dysfunction secondary to radical retropubic prostatectomy for cancer is approximately 100% in the absence of bilateral nerve sparing, and approximately 50% after bnsrrp.

The erectile deficit secondary to bnsrrp is due to transection of the accessory pudendal arteries which act as the main cavernous arteries or is due to incomplete safeguarding of the nerves.

Early intracavernous injection of alprostadil significantly enhances the restoration of erectile function after bnsrrp. The use of selective 5-phosphodiesterase inhibitors has recently been introduced for the therapy of erectile dysfunction secondary to rrp or bnsrrp.

Vardenafil, tadalafil and sildenafil (Urology 2000; 55: 241-245) permit recovery of sexual function in approximately 15% of patients undergoing rrp, or in approximately 45% of patients undergoing bnsrrp.

In the medical field the use of acetyl L-carnitine and propionyl L-carnitine is already known.

WO03047563 describes the use of propionyl L-carnitine, alone or in combination with sildenafil, for the treatment of erectile dysfunction.

EP0539336 describes the use of L-carnitine and a number of alkanoyl L-carnitines for the treatment of idiopathic oligoasthenospermia.

US 5,863,940 describes the use of L-carnitine in combination with acetyl L-carnitine for the treatment of idiopathic oligoasthenospermia.

WO03084526 describes the combined use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine for the treatment of oligoasthenospermia.

US 6,653,349 describes the use of acetyl L-carnitine in combination with propionyl L-carnitine for the treatment of renal dysfunctions.

Numerous other patents and publications describe the use of acetyl L-carnitine and propionyl L-carnitine for therapeutic and/or nutritional purposes, but none of the documents cited above describe these compounds as agents useful for enhancing the efficacy, for example, of sildenafil in the treatment of erectile dysfunction secondary to all those conditions in which there is distress or iatrogenic damage of the lesser pelvis within which the neurovascular bundles of the penis run.

Other compounds useful for the treatment of erectile dysfunction are also known.

For example, in *Int. Urol. Nephrol* 2001; 32 (3), 403-7 the use of sildenafil for the treatment of erectile dysfunction is described.

In *Salute Europa* dated 06/11/2001 are presented the first data, published in the *British Journal of Urology*, regarding the experimentation in Italia and Europe with sublingual apomorphine for the treatment of erectile dysfunction.

Numerous other publications describe the use of compounds useful for the treatment of erectile dysfunction, none of which describe the use of acetyl L-carnitine and propionyl L-carnitine as agents useful for enhancing the efficacy of sildenafil in the treatment of erectile dysfunction according to the present invention.

The drugs known to be useful for the treatment of E.D. are not free of drawbacks.

For example, in *Eur. Urol.* 2001 Aug; 40 (2) : 176-80 it is reported that not all patients respond to treatment with sildenafil.

In *Salute Europa* dated 06/11/2001 it is reported that not all patients respond to treatment with apomorphine.

In *Hosp. Med.* 1998 Oct; 59 (10): 777 and in *Br. J. Urol.* 1996 Oct; 78(4): 628-31 it is reported that the administration of prostaglandin E1 and papaverine, respectively, is performed via the intracavernous route, and the discomfort caused by such administration is well known.

There is therefore a strongly perceived need for the availability of new drugs for the treatment of erectile dysfunction which do not present the drawbacks of the known drugs mentioned above.

It has now been found that the use of acetyl L-carnitine in combination with propionyl L-carnitine, or one of their pharmaceutically acceptable salts, enhances the efficacy of drugs known to be useful for the

treatment of erectile dysfunction secondary to all those conditions in which there is distress or iatrogenic damage of the lesser pelvis within which the neurovascular bundles of the penis run.

What is meant by pharmaceutically acceptable salt of acetyl L-carnitine and propionyl L-carnitine is any salt prepared by addition of an acid to the acetyl L-carnitine or propionyl L-carnitine inner salt, and which does not give rise to unwanted toxic or side effects. The formation of salts by addition of acids is a well known practice in pharmaceutical technology.

Non-limitative examples of these salts are: chloride, bromide, orotate, aspartate, acid aspartate, citrate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate, acid fumarate, magnesium fumarate, glycerophosphate, lactate, maleate and acid maleate, mucate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate, acid tartrate, magnesium tartrate, 2-amino ethanesulphonate, magnesium 2-amino ethanesulphonate, methane-sulphonate, choline tartrate, tricloroacetate, and trifluoroacetate.

One subject of the present invention is therefore the combination of acetyl L-carnitine, propionyl L-carnitine, or one of their pharmaceutically acceptable salts, with one or more drugs useful for the treatment of erectile dysfunction. Non-limitative examples of said drugs useful for the treatment of erectile dysfunction are: sildenafil, vardenafil, tadalafil apomorphine, prostaglandin E1, phentolamine, and papaverine, in their various pharmaceutical preparations.

A further subject of the present invention consists in pharmaceutical and/or dietetic compositions containing as their active ingredient acetyl L-

carnitine, propionyl L-carnitine, or one of their pharmaceutically acceptable salts, in combination with one or more of said drugs useful for the treatment of erectile dysfunction, and at least one pharmaceutically acceptable excipient and/or diluent.

A further subject of the present invention is the use of acetyl L-carnitine and propionyl L-carnitine, or one of their pharmaceutically acceptable salts, for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction.

A further subject of the present invention is the use of acetyl L-carnitine and propionyl L-carnitine, or one of their pharmaceutically acceptable salts, in combination with one of more of said useful drugs, for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction.

A further subject of the present invention is the use of acetyl L-carnitine and propionyl L-carnitine, alone or in combination with one or more of said useful drugs, for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction secondary to all those conditions in which there is distress, iatrogenic damage or trauma of the lesser pelvis within which the neurovascular bundles of the penis run, in which said damage is caused, for example, by radical retropubic prostatectomy without bilateral saving of the neurovascular bundles; by bilateral nerve-saving radical retropubic prostatectomy; by prostate irradiation for cancer; or by rectal surgery.

The following examples illustrate the invention.

EXAMPLE 1

To assess the activity of the combination according to the invention for the treatment of erectile dysfunction, a randomised, double-blind placebo-controlled clinical trial was conducted.

The patients entered into the trial had to meet the following inclusion criteria:

- erectile dysfunction secondary to radical retropubic prostatectomy, with or without bilateral sparing of the neurovascular bundles, in patients in whom the prostatectomy had been performed at least 6 months but less than 2 years prior to entry into the clinical trial;

- complete erectile function prior to the prostatectomy (this information had to be confirmed by the partner or documented in the patient's hospital file;

- not on medical treatment for prostate cancer;

- not on treatment for erectile dysfunction before or after prostatectomy;

- normal total and free prostate antigen values;

- involvement in a heterosexual relationship for at least 6 months prior to surgery.

Patients presenting the following characteristics were not included in the trial:

- hormone imbalance;

- patients taking drugs interacting significantly with the study compounds;

- cerebral or cardiac ischaemia episodes during the past 6 months;

- excessive alcohol or cigarette consumption;
- chronic liver disease;
- abnormal liver function (aspartate and alanine transaminase alterations);
- diabetes;
- decompensated hypertension and hypotension;
- prostate cancer.

The patients recruited into the study were divided into two main groups on the basis of whether or not they had undergone bilateral nerve sparing surgery (rrp and bnsrrp).

These two groups were further subdivided into the following subseta:

a) placebo;
b) sildenafil 100 mg;
c) sildenafil 100 mg + propionyl L-carnitine 2 g + acetyl L-carnitine 2 g;
d) propionyl L-carnitine 2 g;
e) acetyl L-carnitine 2 g.
f) propionyl L-carnitine 2 g + acetyl L-carnitine 2 g;
g) sildenafil 100 mg + propionyl L-carnitine 2 g;
h) sildenafil 100 mg + acetyl L-carnitine 2 g.

The carnitines (acetyl L-carnitine and propionyl L-carnitine) were administered orally twice daily (1 g x 2/day).

Sildenafil was administered (as required) and taken 1-2 hours before sexual intercourse at a dose of 100 mg.

The placebo was administered in the place of acetyl L-carnitine and/or propionyl L-carnitine and/or sildenafil.

After 4 months' treatment the following variables were analysed:

1. erectile function (evaluated by "IIEF-15" scores: IIEF = International Index of Erectile Function);
2. satisfaction with sexual intercourse (IIEF-15);
3. orgasm (IIEF-15);
4. general sexual well-being (IIEF-15);
5. recording of nocturnal penile tumescence (NPT) [evaluated with RigiScan (Dacomed-Minnesota). A >70% increase in rigidity compared to baseline at the base of the penis and >60% at the upper end of the penis, a >2 cm increase in circumference at the upper end of the penis and >3 cm at the base were considered "complete erection". The total duration (minutes) of the recording period on three nights was assessed.

The results obtained, evaluated statistically using the ANOVA test, are given in the tables here below.

TABLE 1

Patients undergoing bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp).

Erectile function			
IIEF 15 Score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	11.3±3.6	-
	After therapy	11.7±3.7	-
Sildenafil 100 mg	Before therapy	11.9±4.0	-
	After therapy	21.7±6.8	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	12.5±5.4	-
	After therapy	27.3±4.6	0.05
Propionyl L-carnitine 2g	Before therapy	12.2±3.9	-
	After therapy	18.1±3.2	NS
Acetyl L-carnitine 2g	Before therapy	11.3±3.8	-
	After therapy	17.2±3.5	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	11.6±3.2	-
	After therapy	24.3±2.6	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	11.7±3.3	-
	After therapy	24.1±2.0	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	11.9±3.6	-
	After therapy	23.0±2.0	NS

TABLE 2

Patients undergoing bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp)

Satisfaction with sexual intercourse			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	3.2±1.1	-
	After therapy	3.1±0.6	-
Sildenafil 100 mg	Before therapy	3.1±1.1	-
	After therapy	4.8±2.5	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	3.0±1.4	-
	After therapy	8.9±4.7	0.01
Propionyl L-carnitine 2g	Before therapy	3.2±1.2	-
	After therapy	3.9±1.1	NS
Acetyl L-carnitine 2g	Before therapy	3.1±1.1	-
	After therapy	4.0±1.1	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	3.2±1.3	-
	After therapy	6.1±2.1	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	3.2±1.3	-
	After therapy	6.3±1.6	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	3.2±1.3	-
	After therapy	6.2±1.1	NS

TABLE 3

Patients undergoing bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp)

Orgasm			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	3.1±0.8	-
	After therapy	3.0±0.6	-
Sildenafil 100 mg	Before therapy	3.0±0.9	-
	After therapy	5.9±2.9	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	3.0±1.0	-
	After therapy	8.8±2.6	0.01
Propionyl L-carnitine 2g	Before therapy	3.0±1.1	-
	After therapy	4.1±1.1	NS
Acetyl L-carnitine 2g	Before therapy	3.2±1.1	-
	After therapy	4.0±0.9	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	2.9±0.9	-
	After therapy	6.5±1.1	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	3.1±1.0	-
	After therapy	6.4±1.1	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	3.0±1.1	-
	After therapy	6.3±1.2	NS

TABLE 4

Patients undergoing bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp)

General sexual well-being			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	3.3±0.9	-
	After therapy	2.8±0.7	-
Sildenafil 100 mg	Before therapy	2.7±1.0	-
	After therapy	5.4±2.7	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	2.8±0.7	-
	After therapy	8.6±2.0	0.01
Propionyl L-carnitine 2g	Before therapy	2.9±1.6	-
	After therapy	4.1±0.9	NS
Acetyl L-carnitine 2g	Before therapy	2.9±1.0	-
	After therapy	3.9±1.1	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	2.8±1.1	-
	After therapy	6.4±1.2	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	2.8±0.8	-
	After therapy	3.9±0.9	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	2.9±1.2	-
	After therapy	3.9±0.8	NS

TABLE 5

Patients undergoing bilateral nerve-sparing radical retropubic prostatectomy (bnsrrp)

Recording of nocturnal penile tumescence (NPT)			
Minutes			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	74.3±12.6	-
	After therapy	69.6±18.0	-
Sildenafil 100 mg	Before therapy	70.4±13.2	-
	After therapy	85.9±14.3	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	69.5±11.4	-
	After therapy	110.3±21.3	0.01
Propionyl L-carnitine 2g	Before therapy	68.2±13.5	-
	After therapy	77.1±16.1	NS
Acetyl L-carnitine 2g	Before therapy	70.8±14.9	-
	After therapy	79.0±12.3	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	66.5±14.8	-
	After therapy	101.1±13.0	0.01
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	72.5±14.3	-
	After therapy	93.1±14.8	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	71.4±12.7	-
	After therapy	91.2±12.7	NS

TABLE 6

Patients undergoing radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles.

Erectile function			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	3.5±1.3	-
	After therapy	3.4±2.6	-
Sildenafil 100 mg	Before therapy	3.8±2.9	-
	After therapy	9.2±1.9	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	2.9±1.0	-
	After therapy	14.1±4.9	0.01
Propionyl L-carnitine 2g	Before therapy	3.3±1.1	-
	After therapy	4.0±1.1	NS
Acetyl L-carnitine 2g	Before therapy	3.2±1.1	-
	After therapy	4.1±1.0	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	3.2±1.0	-
	After therapy	10.2±1.1	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	3.4±1.1	-
	After therapy	10.1±1.1	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	3.4±1.2	-
	After therapy	10.3±1.1	NS

TABLE 7

Patients undergoing radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles.

Satisfaction with sexual intercourse			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	2.0±0.8	-
	After therapy	1.6±0.9	-
Sildenafil 100 mg	Before therapy	1.3±0.8	-
	After therapy	2.9±1.6	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	1.5±1.0	-
	After therapy	3.5±0.2	0.05
Propionyl L-carnitine 2g	Before therapy	1.7±0.4	-
	After therapy	1.9±0.6	NS
Acetyl L-carnitine 2g	Before therapy	1.8±0.8	-
	After therapy	1.9±0.6	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	1.8±0.2	-
	After therapy	1.9±0.2	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	1.6±0.7	-
	After therapy	1.9±0.7	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	1.8±0.7	-
	After therapy	1.9±0.6	NS

TABLE 8

Patients undergoing radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles.

Orgasm			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	0.8±0.7	-
	After therapy	0.8±0.6	-
Sildenafil 100 mg	Before therapy	0.9±0.6	-
	After therapy	2.2±0.9	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	0.8±0.7	-
	After therapy	3.2±1.5	0.05
Propionyl L-carnitine 2g	Before therapy	0.7±0.3	-
	After therapy	1.0±0.3	NS
Acetyl L-carnitine 2g	Before therapy	0.8±0.6	-
	After therapy	0.9±0.4	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	0.6±0.3	-
	After therapy	1.7±0.3	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	0.7±0.4	-
	After therapy	1.8±0.6	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	0.9±0.3	-
	After therapy	1.6±0.4	NS

TABLE 9

Patients undergoing radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles.

General sexual well-being			
IIEF 15 score			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	1.2±0.7	-
	After therapy	0.9±0.7	-
Sildenafil 100 mg	Before therapy	1.1±0.8	-
	After therapy	2.4±2.0	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	1.0±0.8	-
	After therapy	4.0±1.7	0.05
Propionyl L-carnitine 2g	Before therapy	1.3±0.5	-
	After therapy	1.4±0.5	NS
Acetyl L-carnitine 2g	Before therapy	1.0±0.4	-
	After therapy	1.2±0.5	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	1.2±0.6	-
	After therapy	1.2±0.5	NS
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	1.1±0.2	-
	After therapy	1.5±0.3	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	1.3±0.5	-
	After therapy	1.2±0.5	NS

TABLE 10

Patients undergoing radical retropubic prostatectomy (rrp) without bilateral sparing of the neurovascular bundles.

Recording of nocturnal penile tumescence (NPT)			
Minutes			
		mean ± s.d.	p< (*vs* sildenafil after therapy)
Placebo	Before therapy	36.2±10.3	-
	After therapy	37.4±10.4	-
Sildenafil 100 mg	Before therapy	37.1±8.5	-
	After therapy	39.1±7.9	-
Sildenafil 100 mg + propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	37.1±9.6	-
	After therapy	58.6±14.6	0.001
Propionyl L-carnitine 2g	Before therapy	35.0±9.1	-
	After therapy	36.4±5.3	NS
Acetyl L-carnitine 2g	Before therapy	37.7±8.8	-
	After therapy	38.2±5.7	NS
Propionyl L-carnitine 2g + acetyl L-carnitine 2g	Before therapy	36.4±8.3	-
	After therapy	50.1±7.1	0.001
Sildenafil 100 mg + propionyl L-carnitine 2g	Before therapy	34.3±6.2	-
	After therapy	35.5±74	NS
Sildenafil 100 mg + acetyl L-carnitine 2g	Before therapy	37.2±6.8	-
	After therapy	35.5±6.8	NS

The results obtained and reported in Tables 1-10 show that there are no significant differences in baseline values in the various groups and that the administration of placebo did not significantly modify these values.

Treatment with the combination according to the invention invariably yielded statistically significantly superior results as compared to the group treated with sildenafil alone in the tests reported in Tables 1-10.

Significantly superior results were obtained in the group treated with the combination of acetyl L-carnitine and propionyl L-carnitine without sildenafil as compared to the group treated with sildenafil alone, in the tests recording nocturnal penile tumescence (Tables 5 and 10). In addition, in the course of the clinical trial a number of patients treated with the combination of acetyl L-carnitine and propionyl L-carnitine, without simultaneously taking sildenafil, reported experiencing improvements and satisfactory sexual intercourse.

Acetyl L-carnitine and propionyl L-carnitine administered singly or separately together with sildenafil never showed statistically significant superior activity compared to the group treated with sildenafil alone.

The combination according to the invention, in any form, may be suitable for administration to human subjects, the preferred administration route being oral administration.

Acetyl L-carnitine and propionyl L-carnitine and the drug useful for the treatment of erectile dysfunction can be formulated together, as a mixture, or can be formulated separately (packaged separately) using known methods.

On the basis of various factors, such as the concentration of active ingredients or the patient's condition, the combination according to the invention can be marketed as a food supplement, a nutritional supplement, or as a therapeutic product on sale with or without a compulsory doctor's prescription.

The combination according to the invention, when in unit dose form, contains from 50 mg to 4 g of acetyl L-carnitine inner salt, and from 4 g to 50 mg of propionyl L-carnitine inner salt, or an equimolar amount of one of their pharmaceutically acceptable salts, and a suitable dose of the drug useful for the treatment of erectile dysfunction.

The dose recommended, according to the present invention, is 2 g/day of acetyl L-carnitine and 2 g/day of propionyl L-carnitine, and 100 mg of sildenafil once or twice a week.

The daily dose will depend, according to the judgement of the primary care physician, on the patient's weight, age and condition. Larger doses of acetyl L-carnitine and propionyl L-carnitine can be administered thanks to the extremely low toxicity of said active ingredients.

The combination according to the present invention can be prepared by mixing the active ingredients with suitable excipients for the formulation of pharmaceutical and/or dietetic compositions which can be administered to human subjects or to animals.

Experts in pharmaceutical technology are familiar with said excipients.

The combination according to the present invention can also additionally contain one or more vitamins and/or natural lipophilic and/or

hydrophilic antioxidants such as, for example, vitamin E, vitamin A, vitamin C, GSH or selenium.

Acetyl L-carnitine, propionyl L-carnitine and sildenafil are known compounds which can be procured at the chemist's shop or pharmacy.

CLAIMS

1. Combination consisting of acetyl L-carnitine and propionyl L-carnitine, or one of their pharmaceutically acceptable salts, and one or more drugs useful for the treatment of erectile dysfunction.
2. Combination according to claim 1, in which said useful drugs are selected from the group consisting of sildenafil, vardenafil, tadalafil, apomorphine, prostaglandin E1, phentolamine and papaverine, in their various pharmaceutical preparations.
3. Combination according to claim 1 in which the pharmaceutically acceptable salt is selected from the group consisting of chloride, bromide, orotate, aspartate, acid aspartate, citrate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate, acid fumarate, magnesium fumarate, glycerophosphate, lactate, maleate and acid maleate, mucate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate, acid tartrate, magnesium tartrate, 2-amino ethanesulphonate, magnesium 2-amino ethanesulphonate, methanesulphonate, choline tartrate, tricloroacetate, and trifluoroacetate.
4. Pharmaceutical and/or dietetic compositions, containing as their active ingredient the combination according to claims 1-3, and at least one pharmaceutically acceptable excipient and/or diluent.
5. Composition according to claim 4 additionally containing one or more vitamins and/or lipophilic and/or hydrophilic antioxidants.

6. Use of acetyl L-carnitine and propionyl L-carnitine, or one of their pharmaceutically acceptable salts, for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction.
7. Use of the combination according to claims 1-3, for the preparation of a medicament and/or dietetic product for the treatment of erectile dysfunction.
8. Use according to claim 6 or 7, for the preparation of a medicament and/or dietetic product, for the treatment of erectile dysfunction secondary to all those conditions in which there is distress, iatrogenic damage or trauma of the lesser pelvis within which the neurovascular bundles of the penis run.
9. Use according to claim 8, in which said distress or iatrogenic damage of the lesser pelvis within which the neurovascular bundles of the penis run is selected from the group consisting of bilateral nerve-sparing radical retropubic prostatectomy, prostate irradiation for cancer, and rectal surgery.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/011238

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/205 A61K31/519 A61K31/4418 A61K31/191 A61K31/4155
A61P15/10

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/054567 A (SIGMA TAU IND FARMACEUTI 'IT!; KOVERECH ALEARDO 'IT!; CAVALLINI GIORGI) 1 July 2004 (2004-07-01)	6,8,9
Y	claims 1-9 page 3, paragraph 6 tables 2-20	1-5,7
Y	WO 03/047563 A (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A; KOVERECH, ALEARDO; LE) 12 June 2003 (2003-06-12) cited in the application examples 1,2 claims 5,6	1-9
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[X] Further documents are listed in the continuation of box C.

[X] 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

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"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

"X" 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

"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	Date of mailing of the international search report
9 January 2006	30/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/011238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	CAVALLINI G ET AL: "Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging." UROLOGY. APR 2004, vol. 63, no. 4, April 2004 (2004-04), pages 641-646, XP002361866 ISSN: 1527-9995 abstract page 646, column 1, last paragraph; table 1	1-9
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