Composition comprising L-carnitine or an alkanoyl L-carnitine and NADH and/or NADPH

The present invention relates to a composition which exerts an action both on the metabolism and energy performance of skeletal muscle and on the regulation of muscle movement and co-ordination at central level through potentiation of effects at both peripheral muscle and central nervous system level. Accordingly, the composition may take the form and exert the action of a dietary supplement or of an actual medicine, depending upon the support or preventive action, or the strictly therapeutic action, which the composition is intended to exert in relation to the particular individuals it is to be used in.

In particular, as a dietary supplement or preventive agent, the composition of the invention is particularly suitable both for facilitating adaptation of skeletal muscle in individuals engaging in intense, prolonged physical activity and to combat the sensation of muscle fatigue and exhaustion experienced by asthenic subjects even in the total absence of any form of more or less intense physical activity.

Anyone who engages in sports activities, whether professionally or as an amateur, wishes to achieve in a short space of time, and then maintain for as long as possible, the maximum degree of adaptation of the skeletal muscles to the ability to sustain prolonged periods of intense physical activity. The quest for this optimal state of fitness may lead to the inappropriate use of drugs, particularly steroids. It is well known that such drugs can enhance protein synthesis and consequently potentiate the growth of muscle mass to a greater extent than can be achieved with training and diet. The use of these drugs is, however, both illegal and unquestionably harmful when practised in professional sport.

Clearly, then, the only way to achieve the above-mentioned objective properly consists in undergoing appropriate training programs

combined with suitable diets, potentiated through the addition of appropriate dietary supplements.

What is meant here by the term "asthenia" is the diffuse set of aspecific symptoms typical of the stressful life conditions currently prevailing particularly in the major conurbations and built-up areas and involving a vast population, largely regardless of factors relating to age and social status, characterised by a lack or loss of muscular strength, with easy fatigability and inadequate reaction to stimuli.

When used as a strictly therapeutic agent, one particular application of the composition of the invention is in the treatment of chronic fatigue syndrome and Parkinson's disease and of a syndrome similar to idiopathic parkinsonism, induced by the administration of illicit drugs.

Chronic fatigue syndrome (CFS), officially described for the first time in 1988 in *Annals of Internal Medicine*, is a disease characterised by a degree of tiredness not explained by any known cause, often much more intense than that encountered in very serious diseases, such as tumours and AIDS, and debilitating to the extent of causing a more than 50% reduction in working activity and normal social relations, lasting more than 6 months.

According to the criteria outlined in *Annals of Internal Medicine* (December 1994) for diagnosing CFS, the patient must present at least four of the following eight symptoms persistently over a period of 6 months:

1. neuropsychological disorders such as memory loss, excessive irritability, mental confusion, difficulty with thinking and concentrating;
2. pharyngitis;
3. palpable, tender cervical or axillary lymph glands;
4. muscle pain;
5. migratory arthralgia without, however, any swelling of the joints;

6. generalised headache different in type, characteristics and severity from any headaches the patient experienced prior to the disease;
7. sleep disorders, characterised by insomnia or hypersomnia or drowsiness;
8. generalised fatigability and malaise lasting for 24 hr or more after physical activities at levels which were easily tolerated previously.

It is well known that, though Parkinson's disease is generally regarded as an idiopathic condition, the symptoms of parkinsonism can result from the abuse of drugs such as phenothiazine, butyrophenones and reserpine. More recently, parkinsonism has been studied in drug abusers injecting themselves with compounds similar to meperidine, the abusive synthesis of which had produced MPTP and MPPP.

In fact, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP or NMPTP) and 1-methyl-4-phenyl-propoxy-piperidine (MPPP) selectively destroy the dopaminergic neurones in the *substantia nigra* and induce a syndrome both in man and in primates other than man which is entirely similar to idiopathic Parkinson's disease as regards its clinical, pathological and biochemical aspects and its pharmacological responses.

The similarity between idiopathic Parkinson's disease and MPTP-induced parkinsonism is so great that it has been postulated (Burns *et al.*: The neurotoxicity of 1-methyl-4-phenyl-1,2,3.6-tetrahydropyridine in the monkey and man. *Can. J. Neur. Sci.*, 11, n. 1 (supplement), 166-168, February 1984) that this induced parkinsonism "may constitute more than a model. MPTP-induced parkinsonism suggests a putative toxic cause for Parkinson's disease".

The therapy of choice for the management of Parkinson's disease is currently based on the administration of levo-dopa (L-dopa), the metabolic precursor of dopamine, which in itself is incapable of crossing the blood-brain barrier.

Since levo-dopa is extensively metabolised before it is able to reach the sites of action in the brain, it should be administered at very high doses. L-dopa is thus administered in combination with carbidopa, an inhibitor of dopa decarboxylase which prevents the systemic metabolism of levo-dopa before the latter reaches the brain.

When levo-dopa is administered alone, side effects may occur such as anorexia, nausea and vomiting and orthostatic hypotension, which are, however, substantially relieved as soon as carbidopa is administered as well.

After a few months of therapy with L-dopa, however, even when combined with the decarboxylation inhibitor, other very troublesome side effects are possible and frequent: dyskinetic movements of the face, trunk and limbs. The onset of such movements, in most cases, indicates that the drug dosage has reached a critical threshold which must not be exceeded.

There is therefore a strongly perceived need for a support/preventive/ therapeutic agent which, as a result of its efficacy, substantial non-toxicity and lack of side effects, can be safely used by such a broad range of users both in cases simply requiring an appropriate food supplement and at initial onset of symptoms in the above-mentioned pathological conditions.

These multiple goals - to produce a support, preventive and strictly therapeutic agent - are achieved by the composition of the invention, which, as will be described in detail here below, consists in a new combination comprising as its basic ingredients L-carnitine or a lower C2-C6 alkanoyl-L-carnitine or their pharmacologically acceptable salts and nicotinamide adenine dinucleotide (NADH) or a NADH precursor and/or nicotinamide adenine dinucleotide phosphate, reduced form (NADPH).

Over the decades elapsing since the basic discovery (Fritz I.B.: The metabolic consequences of the effects of carnitine on long-chain fatty acid oxidation. Edited by F.C. Gran, New York, Academic Press, 1968, pp. 39-63) that L-carnitine is unique in performing a vital physiological role as a vector of long-chain fatty acids across the internal mitochondrial membrane into the mitochondrial matrix, which is the site of their oxidation, and since a primary deficiency of L-carnitine was first recognised (Engel and Angelini, *Science*, 1973, 179: 899-902) as the cause of a severe, sometimes fatal, though rare, form of myopathy (lipid storage myopathy), there have been enormous advances in our knowledge of the pathological consequences of primary and secondary L-carnitine deficiencies and, conversely, of the therapeutic and nutritional value of an exogenous supply of L-carnitine.

Carnitine is present in all biological tissues in relatively high concentrations as free carnitine and in lower concentrations in the form of acyl carnitines which are metabolic products of the reversible reaction:



catalysed by three groups of enzymes, i.e. the transferases which mainly distinguish themselves by virtue of their specificity for reagent substrates: the carnitine acetyl transferase (CAT) group whose substrate are the short-chain acyl groups (such as acetyl and propionyl); the carnitine octanoyl transferase (COT) group whose substrate comprises the medium-chain acyl groups; and the carnitine palmitoyl transferase (CPT) group whose substrate comprises the long-chain acyl groups.

The important role of carnitine in intermediate metabolism, with particular reference to its limited biosynthesis, serves to explain how a carnitine deficiency may occur as a secondary event in various pathological functions involving different organs and systems. The broadening of the clinical spectrum is reflected in the increasing number of therapeutic opportunities related to the efficacy of this natural compound; the whole scope and range of this efficacy was

revealed when it was observed that L-carnitine replacement therapy dramatically reverses the clinical picture in patients suffering from lipid storage myopathy. The Food and Drug Administration (FDA) have not only accorded L-carnitine the status of an "orphan drug", but have also included it in their list of "life-saving" drugs.

The advances in our knowledge of the pathological implications of primary and secondary carnitine deficiency have been accompanied by a very substantial upsurge in scientific and patent publications mainly focusing on L-carnitine and, to a considerably lesser extent, on some of the acyl carnitines.

Confining ourselves to a partial survey of the patent situation, the use of L-carnitine has been proposed in the cardiovascular field for the treatment of cardiac arrhythmias and congestive heart failure (US 4,656,191), myocardial ischaemia and myocardial anoxia (US 4,649,159); in the field of disorders of lipid metabolism, for the treatment of hyperlipidaemias and hyperlipoproteinaemias (US 4,315,944) and for normalising an abnormal HDL:LDL-VLDL ratio (US 4,255,449); in the field of total parenteral nutrition (US 4,254,147 and US 4,320,145); in nephrology, to counter myasthenia and onset of muscle cramps caused by carnitine losses in dialysis fluid in chronic uraemic patients undergoing regular haemodialytic treatment (US 4,272,549); to counter the toxic effects induced by anticancer agents such as adriamycin (US 4,400,371 and US 4,713,370) and by halogenated anaesthetics such as halothane (US 4,780,308); in the treatment of venous stasis (US 4,415,589); in countering the deterioration of a number of biochemical and behavioural parameters in elderly subjects (US 4,474,812); for normalising triglyceride and tumor necrosis factor (TNF-α) levels in patients with AIDS and in asymptomatic HIV-positive patients (US 5,631,288).

The use of L-carnitine has also been proposed in combination with other active ingredients, such as the L-carnitine coenzyme Q10 combination with a broad spectrum of metabolic/anti-atherosclerotic

action (US 4,599,232).

As regards the alkanoyl L-carnitines, the use of acetyl L-carnitine is known for the treatment of central nervous system diseases, particularly Alzheimer's disease (US 4,346,107) and for the treatment of diabetic neuropathy (US 4,751,242), whereas propionyl L-carnitine has been proposed for the treatment of peripheral vasculopathy (US 4,343,816) and congestive heart failure (US 4,194,006).

Equally complex is the activity exerted by the coenzyme nicotinamide adenine dinucleotide (NADH) whose role at the energy level is well known.

Its function in the respiratory chain is essential for the transport of electrons in the mitochondrial system and in the formation of ATP. Two NADH dehydrogenases have been isolated from the internal mitochondrial matrix. The one with the lower molecular weight (M.W. 78,000), which is probably a subunit of the larger complex (M.W. above 300,000) is regarded as the naturally occurring functional form of the system.

The various complexes located in the internal mitochondrial membrane constitute a chain of oxidative systems going under the name of the cytochrome and Coenzyme Q10 chain, allowing the electrons to be transported from a lower- to a higher-potential system with the use of oxygen and formation of ATP. It is, in fact, from the respiratory chain that the oxidative phosphorylation derives which leads from NADH to the production of ATP.

NADH, along with the cytochrome and Coenzyme Q10 complexes, are the elements necessary for the transformation of energy to ATP and the NADH to be found at the start of this chain is the main conditioning element in this process.

The enzymatic function of NADH is not merely detectable in the energy-type reaction for the formation of ATP, but NADH has also recently been shown to act as a coenzyme necessary for quinodihydroxy-pteridine reductase (DHPR) to proceed with the biosynthesis of H4-biopterin.

The possibility of stimulating the biosynthesis of H4-biopterin and of increasing its concentration in the brain was recently proposed as a way of increasing L-dopa and thus dopamine which present deficiencies in diseases such as parkinsonism, these deficiencies being regarded as underlying the parkinsonian neuropathy. Whereas L-dopa can act as a precursor of dopamine and thus transform itself metabolically into this latter substance, the same does not happen in the case of tyrosine, which can also be regarded as a precursor capable of leading to the formation of L-dopa, without the presence of tyrosine hydroxylase. A reduction in this enzyme has, in fact, been found at the level of the *substantia nigra* of parkinsonian subjects. A reduction in hydroxytyrosine would, moreover, be accompanied a powerful reduction in H4-biopterin, a coenzyme necessary for the synthesis of hydroxytyrosine. Since H4-biopterin does not cross the blood-brain barrier and the direct administration of H4-biopterin is therefore of no avail, it appeared to be useful, in contrast, to resort to stimulation of the formation of H4-biopterin by administering the coenzyme necessary for the activity of quinodihydroxy-pteridine reductase (DHPR) for the formation of H4-biopterin, a function which is known to be performed by NADH. Administration of NADH therefore activates DHPR leading to the formation of the H4-biopterin necessary, in turn, for activating tyrosine hydroxylase so as to achieve the neosynthesis of dopa.

Clinical trials based on intravenous administration of NADH to subjects suffering from Parkinson's disease have confirmed the validity of the theoretical assumptions outlined here above, showing a significant improvement in Parkinson's symptoms in subjects thus treated.

Largely comparable results have been achieved with oral administration of NADH, taking care to administer it using delayed-release gastrointestinal capsules so as to avoid the acid milieu of the stomach which would lead to a rapid reduction in NADH levels.

Clinical improvements in Alzheimer's disease and in chronic fatigue syndrome (CFS) have also been reported with NADH administration (Birkmayer J.G., *Annals Clin. Lb. Sci.*, 26, 1 1996).

On the basis of the characteristics of the compounds described above, the possibility of interaction between them was assessed by means of a series of tests performed on combinations of L-carnitine or its alkanoyl derivatives and NADH and/or NADPH. By means of the tests performed on these new combinations, a surprising, unexpected synergistic interaction was observed between the components of the combinations, which was thoroughly unpredictable on the basis of our pharmacological knowledge of L-carnitine or its alkanoyl derivatives and NADH and NADPH.

The composition of the invention comprises the following components in combination:

(a) L-carnitine or an alkanoyl L-carnitine in which the straight- or branched-chain alkanoyl group has 2-8, and preferably 2-6 carbon atoms, or one of their pharmacologically acceptable salts;
(b) NADH or a NADH precursor and/or NADPH; and
(c) a pharmacologically acceptable excipient.

Preferably, the NADH precursor is nicotinamide.

The weight-to-weight ratio of (a) to (b) generally ranges from 1:0.01 to 1:1, and should preferably range from 1:0.05 to 1:0.5; for example, the weight-to-weight ratio may be 1:0.1.

The alkanoyl L-carnitine should preferably be selected from the group comprising acetyl L-carnitine, propionyl L-carnitine, butyryl L-

carnitine, valeryl L-carnitine and isovaleryl L-carnitine. Acetyl L-carnitine and propionyl L-carnitine are particularly preferred.

For the purposes of the present invention, what is meant by L-carnitine, acetyl L-carnitine, propionyl L-carnitine and isovaleryl L-carnitine is these compounds in the form of inner salts.

What is meant by pharmacologically acceptable salt of L-carnitine or of an alkanoyl L-carnitine is any salt of these with an acid that does not give rise to unwanted toxic or side effects. These acids are well known to pharmacologists and to experts in pharmacy.

Non-limiting examples of such salts, are: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; orotate; oxalate, acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

A list of FDA-approved pharmacologically acceptable salts is to be found in *Int. J. Pharm.* 33, (1986), 201-217, which is incorporated herein by reference.

The composition of the invention may further comprise vitamins, coenzymes, mineral substances and antioxidants.

In unit dosage form, the compositions of the invention comprise, for instance, 100-500 mg of (a) L-carnitine or alkanoyl L-carnitine or an equivalent amount of one of their pharmacologically acceptable salts and a quantity by weight of (b) NADH or NADPH such that the weight-to-weight ratio (a):(b) ranges from 1:0.01 to 1:1, and preferably from 1:0.02 and 1:0.2.

Reference will be made here below, for the sake of simplicity, only to the combination of L-carnitine and NADH, it being understood,

however, that combinations of L-carnitine and NADPH or of the above-mentioned alkanoyl L-carnitines and NADH and/or NADPH are equally effective, fully achieving the objectives of the present invention.

Toxicology tests

Both carnitine and NADH are known to possess only limited toxicity and good tolerability. These favourable characteristics were confirmed by intravenously administering both to rats and to mice combinations of up to 100 mg/kg of L-carnitine and 5 mg/kg of NADH. In prolonged (30-day) toxicity tests, the oral administration of a combination of 250 mg/kg of L-carnitine and 10 mg of NADH was well tolerated and produced no evidence either of mortality or of toxicity or intolerance in the treated animals. Blood-chemistry and histological investigations performed in various organs at the end of treatment revealed no abnormalities as compared to control animals, thus confirming the good tolerability of the combination studied.

Tests on increase in muscle enzymes after prolonged exercise

To assess the effect of carnitine and NADH as well as of a combination of the two on the concentration of mitochondrial enzymes involved in muscular exercise, tests were carried out to establish whether the activity of these mitochondrial enzymes in the gastrocnemius muscle of rats subjected to prolonged muscular exercise could be increased as compared to control animals in response to the greater energy demand required by prolonged muscular effort. To this end a group of Wistar rats was subjected to muscle training by placing them on a Rotaroid apparatus (Basile, Como, Italy) at a rate of 20 m/min for 120 min every day (Benzi G., *J. Appl. Physiol.*, 38, 565, 1975). Muscle enzyme activity was assessed after seven or after thirty days' training following isolation and homogenising of the gastrocnemius muscle of each rat (Oscai L.B., *J. Biol. Med.*, 245, 6968, 1971). The enzymes assessed were citrate synthetase, isocitrate dehydrogenase and succinate dehydrogenase.

The results obtained in this test demonstrated that the combination of carnitine and NADH was capable of inducing a very significant increase in enzyme activity after only seven days of training, whereas at this observation time no changes induced by either carnitine or NADH alone were detected as compared to controls.
The strong synergistic effect of these two products was even more marked after thirty days' training.

Treatment	Days' Training	Citrate synthetase	Isocitrate dehydrogenase	Succinate dehydrogenase
Controls	0	20.9±1.4	2.25±0,31	3.70±0,22
Controls	7	22.1±1.6	2.30±0.20	3.90±0.19
Controls	30	29.9±2.1	3.33±0.20	5.20±0.30
Carnitine 250 mg/kg	0	20.8±0.95	3.05±0.19	3.35±0.35
Carnitine 250 mg/kg	7	22.6±1.9	2.85±0.31	3.85±0.45
Carnitine 250 mg/kg	30	30.1±0.95	2.98±0.16	4.90±0.33
NADH 10 mg/kg	0	21.5±1.4	2.35±0.29	3.60±0.21
NADH 10 mg/kg	7	30.5±2.5	3.65±0.55	4.15±0.45
NADH 10 mg/kg	30	33.6±2.1	3.55±0.36	5.40±0.45
Carnitine 250 mg/kg + NADH 10 mg/kg	0	21.4±1.9	2.15±0.18	3.80±0.22
Carnitine 250 mg/kg + NADH 10 mg/kg	7	47.7±3.92	5.1±0.29	7.15±0.30
Carnitine 250 mg/kg + NADH 10 mg/kg	30	75.9±3.51	6.3±0.5	9.25±0.65

(*) Enzymatic activity is expressed as µmol of substrate used per min/g tissue weight

Tests on increase in rabbit papillary muscle ATP concentrations after hypoxia

These tests were used to assess whether L-carnitine and NADH or a combination of the two were capable of preserving ATP concentrations of rabbit heart papillary muscle after subjecting the rabbit to hypoxia, which is known to lead to depletion of this energy compound. The tests were conducted on New Zealand rabbits which received intravenous injections of both L-carnitine (100 mg/kg) and NADH (10 mg/kg) alone,

as well as of the two substances in combination, every day for three consecutive days.

Another group of animals served as a control group receiving no treatment. At the end of the third day of treatment all animals were sacrificed, their hearts were extracted and sections of papillary muscle measuring 1 mm in diameter and 4.5 mm in thickness were isolated. The tissues thus isolated were perfused in a thermostatic bath with a 100% saturated O_2 solution. The experimental hypoxia was then produced by introducing 100% N_2 in the bath in place of O_2. The ATP content of the papillary muscle was analysed using the method described by Strehler B.L. (Strehler B.L., Methods in Enzymology III. New York. Acad. Press, 871, 1957). The analysis was carried out on tissue samples maintained under normal perfusion for a period of 90 min and after a period of hypoxia also lasting 90 min.

These tests showed that the ATP concentrations were substantially diminished both in control animals and in the animals treated with either carnitine alone or NADH alone. In the animals treated with the combination of carnitine and NADH, on the other hand, complete protection against the ATP reduction induced by hypoxia was found.

These tests were therefore able to reveal the ability of the combination of L-carnitine and NADH to protect the ATP present in papillary muscle against a reduction induced by hypoxia to an extent which could not be achieved either with L-carnitine alone or with NADH alone, but which, surprisingly, can be achieved with the combination.

Treatment	ATP concentration (mol/g tissue)	
	Before hypoxia	After hypoxia
Controls	1.54±0.31	0.40±0.051
Carnitine 100 mg/kg	1.65±0.28	0,55±0.031
NADH 10 mg/kg	1.60±0.30	0,65±0.044
Carnitine 100 mg/kg + NADH 10 mg/kg	1.90±0.37	1,52±0.061

Tests on the ability of L-carnitine and NADH to stimulate dopamine production

These tests were performed on neuroblastoma cell cultures with a cell concentration ranging from 15-30 to 60 million, incubated with 200 µg of NADH/ml or with 2 mg/mL of L-carnitine or with the two components in combination.

The production of dopamine induced by NADH and L-carnitine was assayed by HPLC according to the Mayer method (Mayer G.S., Strong R.F., *Current separation* 4, 44, 1982) modified by Jonsson and Keller (Jonsson G., Holman H., Adams R.N., Central adrenaline neurones. Ed. De Fuxe-Pergamon Press, 59, 1980; Keller R., Oke A., Mefford I., *Life Sciences*, 19, 995, 1976). The results of these tests demonstrate that addition of NADH to the cell culture effectively induces an increase in dopamine production related to the number of cells present.

A significantly greater increase is obtainable, however, when L-carnitine, which alone produces only a very slight effect, is added to the NADH solution. The synergistic effect is therefore marked in these tests, too.

Percentage increase in dopamine synthesis in neuroblastoma cell cultures incubated with NADH or with carnitine as a function of the number of cells incubated (millions)

Treatment	N. cells (millions)	% increase	N. cells (millions)	% increase	N. cells (millions)	% increase
NADH 100 µg/mL	15	4.5	30	31,5	60	45.5
NADH 200 µg/mL	15	11.8	30	40,6	60	55.6
Carnitine 1 mg/mL	15	---	30	2,1	60	5.6
Carnitine 2 mg/mL	15	---	30	3,3	60	6.6
NADH 100 µg/mL + Carnitine 1 mg/mL	15	6.6	30	45,2	60	50.6
NADH 200 µg/mL + Carnitine 2 mg/mL	15	18.4	30	56,4	60	70.5

MPTP (1-methyl-4-phenyl-1,2,3,6.tetrahydropyridine) test

The use of MPTP as a neurotoxin mainly active at the level of the neuroskeletal system may be a significant experimental model for the study of parkinsonism and its biochemical and clinical pathogenesis.

In both the monkey and the mouse, high doses of MPTP (40 mg/kg) induce the hypokinetic and bradykinetic symptoms typical of Parkinson's disease accompanied by an appreciable reduction of dopa and its metabolites. In these tests, it was studied whether the behavioural and motility damage induced by MPTP in the mouse, as well as the dopamine concentrations, could be modified and corrected by the administration of NADH or L-carnitine alone or of both substances in combination.

For these tests black mice of the C57 BE/6 strain with a body weight of 20 g were used; one group of these mice were kept as controls, while the other groups were injected with two injections of 40 mg/kg MPTP subcutaneously with a 24 hr interval. Three weeks after the MPTP injection the motility of all the treated animals and the control animals was evaluated. The dopa assay was also carried out three weeks after MPTP treatment. Treatment both with NADH and with carnitine was given immediately prior to the start of the motility test; motility was assessed using a plexiglas camera traversed at different heights by two infrared rays according to the procedure described by Archer (Archer T., Fredrikson A., *Psychopharmacology*, 88, 141, 1986).

The reduction in motility induced by MPTP proved greater than 80% in the control mice, and motility was reduced by 60% and 70% by NADH and L-carnitine alone, respectively, while with the combination of the two substances motility was restored to practically normal levels (20% reduction). Also of interest were the results for dopa concentrations in striated muscle, which were reduced by 90% in control mice administered MPTP, but presented almost normal levels in the treated mice. In these tests, too, while the effect of L-carnitine alone appeared

to be almost negligible and that of NADH was equal to 40%, the combination restored dopa to levels very close to the concentrations normally present in this tissue.

Some examples of compositions according to the invention are reported here below:

(1)	L-carnitine inner salt	mg	200
	NADH	mg	5
(2)	L-carnitine inner salt	mg	200
	NADH	mg	10
(3)	Acetyl L-carnitine inner salt	mg	250
	NADH	mg	5
(4)	Acetyl L-carnitine inner salt	mg	500
	NADH	mg	10
(5)	Propionyl L-carnitine inner salt	mg	250
	NADH	mg	5
(6)	L-carnitine inner salt	mg	200
	NADH	mg	5
	Coenzyme Q10	mg	20
	Pyridoxine	mg	3
	Selenium	mg	20
	Zinc	mg	2
(7)	L-carnitine inner salt	mg	200
	NADH	mg	5
	Coenzyme Q10	mg	20
	Taurine	mg	10
	Inosine	mg	100
	Creatine	mg	100
	Piruvic acid	mg	10

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Claims

1. A composition which comprises:
(a) L-carnitine or alkanoyl L-carnitine wherein the alkanoyl group, straight or branched, has 2-8, preferably 2-6 carbon atoms, or a pharmacologically acceptable salt thereof;
(b) nicotinamide adenine dinucleotide, reduced form (NADH) or a precursor thereof, and/or nicotinamide adenine dinucleotide phosphate, reduced form (NADPH); and
(c) a pharmacologically acceptable excipient.

2. The composition of claim 1, wherein the NADH precursor is nicotinamide.

3. The composition of claim 1 or 2, wherein the weight ratio (a):(b) is from 1:0.01 to 1:1.

4. The composition of claim 3, wherein the weight ratio (a):(b) is from 1:0.02 to 1:0.2.

5. The composition of claim 4, wherein the weight ratio (a):(b) is 1:0.1.

6. The composition of claims 1-5, wherein the alkanoyl L-carnitine is selected from the group comprising acetyl L-carnitine, propionyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine.

7. The composition of any of the preceding claims wherein the pharmacologically acceptable salts is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; orotate; oxalate; acid oxalate; sulphate, acid sulphate;

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trichloroacetate; trifluoroacetate and methane sulphonate.

8. The composition of any of the preceding claims, which further comprises vitamins, coenzymes, mineral substances and antioxidants.

9. The composition of claim 1 or 2, in unit dosage form, which comprises 100-500 mg of (a) L-carnitine or alkanoyl L-carnitine or an equivalent amount of a pharmacologically acceptable salt thereof and an amount of (b) NADH, NADH precursor or NADPH such that the weight ratio (a):(b) is from 1:0.01 to 1:1.

10. The composition of claim 4, in unit dosage form, which comprises 100-500 mg of (a) L-carnitine or alkanoyl L-carnitine or an equivalent amount of a pharmacologically acceptable salt thereof and an amount of (b) NADH, NADH precursor or NADPH such that the weight ratio (a):(b) is from 1:0.02 to 1:0.2.

11. The composition of any of the preceding claims, orally administrable and in the form of a dietary supplement.

12. The composition of any of the preceding claims, orally or parenterally administrable in the form of a medicament.

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