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(71) Applicant: **LABOREST ITALIA S.P.A.** [—/IT]; Via Vicinale di Parabiago 22, I-20014 Nerviano, Milano (IT).

(72) Inventors: **SECONDINI, Lorenzo**; c/o Rode Pharma S.R.L. Duca D'Aosta 3, I-21052 Busto Arisizio (VA) (IT). **AMELOTTI, Luigi**; c/o Rhode Pharma S.R.L., Viale Duca D'Aosta 3, I-21052 Busto Arsizio (VA) (IT).

(74) Agents: **HOFFMAN . EITLE (Dr. Marco Benudetto)** et al.; Arabellastrasse 4, 81925 Munich (DE).

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(54) Title: COMPOSITION FOR USE IN THE TREATMENT OF POLYCYSTIC OVARY SYNDROME

(57) Abstract: The present invention relates to a pharmaceutical composition or a nutraceutical composition or a medical device or a supplement product for use in the preventive and/or curative treatment of polycystic ovary syndrome (PCOS) and of the metabolic disorders deriving from or connected to polycystic ovary syndrome. Moreover, the present invention relates to a pharmaceutical composition or a nutraceutical composition or a medical device or a supplement product for use in reducing the lipid profile and the degree of hirsutism in insulin resistant and hyperandrogenous women affected by polycystic ovary syndrome - PCOS.

***"Composition for use in the treatment of polycystic ovary syndrome"***

The present invention relates to a pharmaceutical composition or a nutraceutical composition or a medical device or a supplement product for use in the preventive and/or curative treatment of polycystic ovary syndrome (PCOS) and of the metabolic disorders deriving from or connected to polycystic ovary syndrome. Moreover, the present invention relates to a pharmaceutical composition or a nutraceutical composition or a medical device or a supplement product for use in reducing the lipid profile and the degree of hirsutism in insulin resistant and hyperandrogenous women affected by polycystic ovary syndrome.

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder which affects 10-15% of the female population. This syndrome represents the most common hormonal disorder in women of reproductive age.

Polycystic Ovary Syndrome (PCOS) is the most frequent endocrinopathy of the female sex in reproductive age and the most common cause of anovulatory infertility.

Above all, it is the main cause of oligo-amenorrhoea. The symptoms and severity of the disease vary greatly among women.

In women with PCOS, the physiological hyperinsulinaemia of adolescence may constitute a triggering factor that brings about the development of hyperandrogenism and anovulation.

Polycystic ovary syndrome has a basic etiology linked to an oxidative syndrome with insulin resistance. The insulin resistance and consequent hyperinsulinaemia that are often associated with this syndrome play an important role not only in the pathogenesis of the syndrome itself, but also in the clinical symptomatology.

The diagnosis of insulin resistance is based on various tests, among which the simplest is the determination of insulin levels, both basal and after OGTT. The formula HOMA, which focuses on the fasting basal levels of glucose and insulin: HOMA = glucose (mmol/l) x insulin (mU/ml) / 22.5. Values > 2.5 indicate insulin resistance.

Moreover, patients with this syndrome have an increased risk of developing pathologies such as type 2 diabetes, the metabolic syndrome in connection with hypertension, dislipidaemia and cardiovascular

diseases, obesity, high plasma levels of C-Reactive Protein (CRP) and triglycerides with low levels of cholesterol.

The use of the active ingredient metformin for treating polycystic ovary syndrome is well known. However, satisfactory results are not always achieved with such treatments.

Reversible gastrointestinal side effects occur in 30% of the cases in patients who take metformin. These include abdominal discomfort characterized by diarrhoea, nausea, abdominal swelling, loss of appetite, anorexia and a metallic taste in the mouth.

At present, there also exist therapies based on preparations capable of correcting the glycaemic/hormonal imbalance and positively influencing the parameters associated with polycystic ovary syndrome, such as acne, hirsutism, metabolic cycle alterations and infertility. However, these therapies, too, fail to give satisfactory results. In fact, as the pathology evolves, there is a known risk deriving from the fact that metabolic imbalances such as insulin resistance and/or dislipidaemia can be amplified.

Thus there remains a need to have a composition capable of effectively influencing, regulating and/or modifying the altered parameters mentioned above.

Furthermore, there remains a need to have new and effective formulations that are capable of treating polycystic ovary syndrome and are capable of treating and/or reducing the metabolic disorders deriving from or connected to polycystic ovary syndrome. It would be desirable to be able to have new and effective formulations also capable of acting on the control of lipid metabolism in women with PCOS, given that the increase in cholesterol is partly tied to the high levels of androgens that are present in women with PCOS and worsen insulin resistance through an anabolizing action.

Finally, there remains a need to have new and effective formulations that do not have any side effects, are well tolerated by the subjects treated and are also easy to administer.

The Applicant has given a response to the above-mentioned needs thanks to a selected combination of active compounds, which unexpectedly show an unexpected mutual synergistic action.

The present invention therefore relates to a pharmaceutical composition or a nutraceutical composition or a supplement product for use in a preventive treatment of polycystic ovary syndrome and/or the metabolic disorders deriving from or connected to polycystic ovary syndrome - said disorders being selected from

among insulin resistance, dislipidaemia and hormonal alterations - and having the characteristics set forth in the appended claim.

The present invention relates to a pharmaceutical composition or a nutraceutical composition or a supplement product for use in a curative treatment for reducing and/or eliminating the symptoms of polycystic ovary syndrome and of the metabolic disorders deriving from or connected to polycystic ovary syndrome - said disorders being selected from among insulin resistance, dislipidaemia and hormonal alterations – and having the characteristics set forth in the appended claim.

Other preferred embodiments of the present invention are set forth in the detailed description that follows, solely by way of example, therefore without limiting the scope of the present invention.

In the context of the present invention, "formulation" means a pharmaceutical composition or a medical device or a nutraceutical composition or a supplement product, in accordance with the present invention.

The formulation of the present invention comprises a mixture which comprises or, alternatively, consists of the compounds (i) and (iii) (binary formulation) in various proportions to each other, as described and/or claimed below. Said mixture is formulated with excipients, technological additives, co-formulations, polar and/or semipolar polymeric matrices, carriers and stabilizers of pharmaceutical or food grade, which must be suitable for preparing a solid formulation, such as, for example, a formulation in powder or granular form, in tablets or in capsules; or a liquid solution; or a suspension in syrup.

The Applicant has found that said mixture comprising or, alternatively, consisting of:
(i) a compound based on red yeast rice (*Monascus purpureus*) in a therapeutically effective amount, and
(iii) a lipoic acid compound or a derivative thereof, in a therapeutically effective amount, is advantageously indicated for use in treatments (a) and (b), as specified below.

The compound based on red yeast rice (*Monascus purpureus*) is titrated in monacolin and is in the form of a powder extract.

The Applicant has found that the formulation of the present invention which comprises said mixture comprising or, alternatively, consisting of the compounds (i) and (iii) (binary formulation) has valid application for use in:

(a) a preventive treatment of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome, having the characteristics as set forth in the appended claim, and/or

(b) a curative treatment for reducing and/or eliminating the symptoms of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome.
The formulation of the present invention comprises a mixture which comprises or, alternatively, consists of the compounds (i), (ii) and (iii) (ternary formulation) in various proportions to one another, as described and/or claimed below. Said mixture is formulated with excipients, technological additives, co-formulations, polar and/or semipolar polymeric matrices, carriers and stabilizers of pharmaceutical or food grade, which must be suitable for preparing a solid formulation, such as, for example, a formulation in powder or granular form, in tablets or in capsules; or a liquid solution; or a suspension in syrup.

The Applicant has found that said mixture comprising or, alternatively, consisting of:
(i) a compound based on red yeast rice (*Monascus purpureus*), in a therapeutically effective amount,
(ii) a D-chiro-inositol and/or myo-inositol compound, in a therapeutically effective amount, and
(iii) a lipoic acid compound or a derivative thereof, in a therapeutically effective amount, is advantageously indicated for use in treatments (a) and (b), as specified below.

In one embodiment, the compound based on red yeast rice (*Monascus purpureus*) is titrated in monacolin, for example it is titrated in monacolin at 3% or 5% or 10%, and is in the form of a powder extract.

The Applicant has found that the formulation of the present invention which comprises said mixture comprising or, alternatively, consisting of the compounds (i), (ii) and (iii) (ternary formulation) has valid application for use in:

(a) a preventive treatment of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome, having the characteristics as set forth in the appended claim, and/or

(b) a curative treatment for reducing and/or eliminating the symptoms of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome.

The significance of preventive treatment for PCOS is tied to the fact that treating subjects with PCOS preventively can correct altered metabolic parameters which represent possible risk factors.

With reference to the preventive treatment as per point (a), it is noted that the combination of the three compounds (i), (ii) and (iii) together acts by improving the entry of glucose into cells, on the consequent reduction in insulin resistance and in reducing LDL cholesterol with a mechanism similar to that of statins.

With reference to the curative treatment as per point (b), it is noted that normalizing the altered parameters reduces the damage they can cause; from the viewpoint of symptoms, any menstrual irregularities, acne and/or hirsutism potentially caused by the alterations are reduced.

The Applicant has noted that monacolin K and myo-inositol are together capable of combating insulin resistance and the increase in cholesterol, as well as being capable of controlling lipid metabolism. Inositol (D-chiro inositol or myo-inositol) enhances its effect thanks to the presence of monacolin K. Monacolin K, or a derivative thereof, by reducing cholesterol, as a precursor of androgen synthesis, can improve the hyperandrogenous symptoms that affect women suffering from this syndrome. Moreover, the presence of lipoic acid, which has a marked antioxidant action through the formation of glutathione, contributes positively. In women with PCOS there is an increased production of free radicals, which contribute to the inflammation that affects these women, exacerbates their symptoms and contributes considerably to making them infertile. Finally, significant results have been obtained with the combination of lipoic acid and monacolin K.

The formulation comprises a mixture which comprises or, alternatively, consists of the compounds (i) and (iii) or, alternatively, the compounds (i), (ii) and (iii) in various proportions by weight to one another, as described and/or claimed below. Said mixture is formulated with excipients, technological additives, co-formulations, polar and/or semipolar polymeric matrices, carriers and stabilizers of pharmaceutical or food grade, which must be suitable for preparing a solid formulation, such as, for example, a formulation in powder or granular form, in tablets or in capsules; or a liquid solution; or a suspension in syrup.

For example, the pharmacologically acceptable excipients are selected from among thickening agents, such as, for example, xanthan gum and guar gum; edulcorants, such as, for example, sorbitol and sucralose; acidifiers, such as, for example citric acid; maltodextrins; anti-agglomerants, such as, for example silicon dioxide and magnesium stearate; antioxidants and flavourings.

The compound based on red yeast rice (*Monascus purpureus*) present in the binary or ternary formulation is obtained using methods and apparatus known to the person skilled in the art. The compound based on red yeast rice (*Monascus purpureus*) is titrated in monacolin, for example it is titrated in monacolin at 3% or 5% or 10%, using methods and apparatus known to the person skilled in the art.

The D-chiro inositol compound (ii), present in the ternary formulation, is also known as 1D-chiro-inositol or D-(+)-chiro-inositol). Examples of D-chiro inositol derivatives or analogues are, for example, pinitol, e.g. D-pinitol, or D-chiro-inositol-phosphate.

The lipoic acid compound present in the binary or ternary formulation contains alpha lipoic acid (thioctic acid 1077-28-7) in the R(+) configuration (R(+) enantiomer) or as a racemic R(+)/S(-) mixture. The racemic mixture can contain the R(+) enantiomer in an amount comprised from 50% to 100%, relative to the lipoic acid present, and the S(-) enantiomer in an amount comprised from 50% to 0%, relative to the lipoic acid present.
The lipoic or alpha lipoic acid (iii) can be present in the binary or ternary formulation only in the form of the R(+) enantiomer, or as a 50/50, or 60/40, 70/30, 80/20 or 90/10 or 100/0 racemic R-(+)-alpha lipoic acid/S-(-)-alpha lipoic acid mixture.

Preferably, the binary or ternary formulation of the present invention contains a 50/50 racemic R-(+)-alpha lipoic acid/S-(-)-alpha lipoic acid mixture.

In the binary or ternary formulations of the present invention, the inositol can be present as myo-inositol in combination with the compound based on red yeast rice (*Monascus purpureus*) (i) and lipoic acid (iii).

Advantageously, the binary or ternary formulation of the present invention contains alpha lipoic acid (iii) in non-dissociated acid form or in the form of a pharmaceutically acceptable salt, for example a sodium salt.

Said excipients (or other substances such as technological additives, co-formulants, polar and/or semipolar polymeric matrices, carriers and stabilizers) are present in an amount comprised from 50 to 20% by weight, relative to the total weight of the binary or ternary formulation, preferably from 40 to 20% by weight, relative to the total weight of the formulation.

In one embodiment, the binary or ternary formulation of the present invention contains a compound based on red yeast rice (*Monascus purpureus*) titrated in monacolin at 3%. In this case one can use from 100 to 500 mg of red yeast rice in a total of 3000 mg of binary or ternary formulation. In this case the red yeast rice is present in the formulation in a percentage by weight comprised from 3.3 to 16%, relative to the final weight of the binary or ternary formulation.

In another embodiment, the binary or ternary formulation of the present invention contains a compound based on red yeast rice (*Monascus purpureus*) titrated at 10% in monacolin. In this case one can use from 10 to 150 mg, for example 100 mg of red yeast rice in a total of 3000 mg of binary or ternary formulation.

In this case the red yeast rice is present in the formulation in a percentage by weight comprised from 0.034 to 5%, relative to the final weight of the formulation.

Said D-chiro inositol or myo-inositol (ii) present in the binary or ternary formulation is present in an amount comprised from 30 to 60% by weight, relative to the total weight of the formulation, preferably from 40 to 50% by weight, relative to the total weight of the ternary formulation. The ternary formulation comprises D-chiro inositol or myo-inositol in an amount comprised from 30 to 60% by weight, relative to the total weight of the formulation, preferably from 40 to 50% by weight, relative to the total weight of the ternary formulation.

Said lipoic acid (iii) present in the binary or ternary formulation is present in an amount comprised from 10 to 35% by weight, relative to the total weight of the formulation, preferably from 15 to 20% by weight, relative to the total weight of the formulation. The binary or ternary formulation comprises alpha lipoic acid in the R(+) configuration (R(+) enantiomer) or as a racemic R(+)/S(-) mixture [where the racemic mixture contains the R(+) enantiomer in an amount comprised from 50% to 100%, relative to the lipoic acid present] in an amount comprised from 5 to 35% by weight, relative to the total weight of the formulation, preferably from 15 to 20% by weight, relative to the total weight of the binary or ternary formulation.

Said D-chiro inositol or myo-inositol compound is administered, via the ternary formulation of the present invention, at a concentration comprised from 0.5 to 5 grams/daily dose, preferably from 1 to 4 grams/daily dose. In a preferred embodiment, there are administered, for example, 2 tablets or 2 sachets per day containing a concentration of 0.6 g of D-chiro inositol or 2 g of myo-inositol per tablet or sachet. Usually, 0.6 g of D-chiro inositol can be substituted with 1 g or else 2 g of myo-inositol.

The binary or ternary formulation of the present invention contains lipoic acid or alpha lipoic acid as the R(+) enantiomer, or as a 50/50 or 60/40, 70/30, 80/20 or 90/10 racemic mixture of R-(+)-alpha lipoic acid and S-(-)-alpha lipoic acid. Preferably, it is a 50/50 racemic mixture.

The lipoic or alpha lipoic acid (iii) is protected to avoid pyrosis in the mouth, esophagus, and stomach (gastric pyrosis) of the subject undergoing treatment. Furthermore, the lipoic or alpha lipoic acid is protected so as to release the lipoic acid in a gradual and controlled manner in the body of the subject treated with the formulation of the present invention.

It is desirable that at least 50%, preferably 60%, of the lipoic or alpha lipoic acid be released in the stomach within 30 minutes after administration and the remaining 50%, preferably 40%, be released in the

gastrointestinal tract. This release mode ensures a level of lipoic or alpha lipoic acid in blood serum for a period comprised from 0 to less than 4 hours.

The gradual release of lipoic acid makes it possible, on the one hand, to obtain levels of lipoic acid in blood serum that are comparable to those that would be obtained with a single injectable dose or with a formulation containing non-controlled release (non-protected) lipoic acid and, on the other hand, to maintain, over a period of time comprised from 0 to less than 4 hours, a level of lipoic acid in blood serum comprised from 20 to 80 ng/ml of plasma, preferably from 30 to 60 ng/ml of plasma, even more preferably from 45 to 55 ng/ml of plasma.

The lipoic or alpha lipoic acid (iii) present in the binary or ternary formulation can be in microencapsulated or coated form (protected form) so as to ensure a gradual and controlled release of lipoic acid in a time interval comprised from 0 to less than 4 hours.

Alternatively, the lipoic or alpha lipoic acid (iii) is present in said binary or ternary formulation not in a microencapsulated or coated form, but rather immersed in a matrix, for example of a polymeric nature, which in any case ensures a gradual and controlled release of the lipoic acid over time, in a time interval comprised from 0 to less than 4 hours (protected form). The choice will depend on the type of pharmaceutical administration it is desired to achieve with the formulation of the present invention.

The binary or ternary formulation of the present invention (pharmaceutical composition or nutraceutical composition or medical device or supplement product or food supplement) is prepared for oral administration, for example in the form of a tablet, granules for tablets or granules for sachets.

In one embodiment, 2 sachets per day or 2 tablets per day are administered, having a formulation as shown below:

(1) A formulation in sachets can have the following composition:
red yeast rice (*Monascus purpureus*) titrated in monacolin at 3%: 150 mg (equal to 4.5 mg of monacolin)
D-chiro inositol: 600 mg, or else myo-inositol: 1000 mg
Lipoic acid: 400 mg

(2) A formulation in tablets can have the following composition:
red yeast rice (*Monascus purpureus*) titrated in monacolin at 5%: 100 mg (equal to 5 mg of monacolin)
D-chiro inositol: 600 mg, or else myo-inositol: 1000 mg
Lipoic acid: 400 mg.

(3) A formulation in sachets can have the following composition:
red yeast rice (*Monascus purpureus*) titrated in monacolin at 3%: 150 mg (equal to 4.5 mg of monacolin)
D-chiro inositol: 600 mg, or else myo-inositol: 2000 mg
Lipoic acid: 400 mg

(4) A formulation in tablets can have the following composition:
red yeast rice (Monascus purpureus) titrated in monacolin at 5%: 100 mg (equal to 5 mg of monacolin)
D-chiro inositol: 600 mg, or else myo-inositol: 2000 mg
Lipoic acid: 400 mg.

If the binary or ternary formulation of the present invention is in tablet form, the lipoic or alpha lipoic acid that is present in said formulation in tablet form is mixed together with polymers, for example polymers selected from among microcrystalline cellulose, hydroxypropyl cellulose and hydroxypropyl methyl cellulose at a different molecular weight, and together with additives such as magnesium stearate, silicon dioxide, talc and dicalcium phosphate so as to achieve a coating that enables a controlled and gradual release of the lipoic acid. The coating is made using apparatus and technologies known to a person skilled in the art, who is undoubtedly capable of selecting the most suitable polymers among those commercially available and the best operating conditions.

Subsequently, once the tablet has been prepared, it is externally coated with a thin layer of a coating or film (film coating) to provide a coated tablet that ensures a controlled and gradual release in a period of from 0 to 4 hours. The external coating of the tablet is realized using apparatus and technologies known to a person skilled in the art, who is undoubtedly capable of selecting the most suitable coating materials or films among those commercially available and the best operating conditions.

For example, a tablet comprising the binary or ternary formulation of the present invention is coated (protected tablet) with a thin layer of a coating or film (film coating) using one or more enteric coatings. The coating or film has a pH-dependent solubility capable of enabling release according to the pH value in a given segment of the gastrointestinal tract, and of ensuring a rapid absorption of the lipoic acid. The enteric coating is realized with coating compounds known to persons skilled in the art, for example hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate or polyvinyl acetate-phthalate.
The coating is applied using apparatus and technologies known to a person skilled in the art, who is undoubtedly capable of selecting the most suitable coating compounds among those commercially available.

In the case of a tablet, it is desirable that at least 50%, preferably 60%, of lipoic or alpha lipoic acid be released in the stomach within 30 minutes after administration and the remaining 50%, preferably 40%, be released in the gastrointestinal tract in the following 3-4 hours. This release mode ensures a level of lipoic or alpha lipoic acid in blood serum for a period comprised from 0 to less than 4 hours. The tablet of the present invention can be said to have a 50/50 fast/slow controlled release.

If the binary or ternary formulation of the present invention is in the form of granules for sachets or for hard gelatine capsules, the lipoic or alpha lipoic acid is present in said formulation in microencapsulated or coated form (encapsulated or coated lipoic acid) to provide a controlled and gradual release in a period of from 0 to 4 hours. In this case, the lipoic acid is microencapsulated or coated (protected form) to a degree of at least 92%, preferably 96%, by weight. The microencapsulation or coating is applied on the lipoic or alpha lipoic acid using apparatus and technologies known to a person skilled in the art, who is undoubtedly capable of selecting the most suitable coating compounds among those commercially available. In one embodiment, the lipoic or alpha lipoic acid is microencapsulated or coated with a combination of lacquer gum, triethylcitrate and talc.

In the case of granules for sachets, it is desirable that at least 50%, preferably 60%, of lipoic or alpha lipoic acid be released in the stomach within 30 minutes after administration and the remaining 50%, preferably 40%, be released in the gastrointestinal tract in the following 3-4 hours. This release mode ensures a level of lipoic or alpha lipoic acid in blood serum for a period comprised from 0 to less than 4 hours. The granules for sachets of the present invention can be said to have a 50/50 fast/slow controlled release.
Said lipoic acid is administered, via the binary or ternary formulation of the present invention, at a concentration comprised from 100 to 1200 milligrams/daily dose, preferably from 300 to 800 milligrams/daily dose. The lipoic acid or alpha lipoic acid is administered, via the binary or ternary formulation of the present invention, at a concentration comprised from 100 to 1200 milligrams/daily dose, preferably from 300 to 600 milligrams/daily dose, as the R(+) enantiomer or as a 50/50 or 60/40, 70/30, 80/20 or 90/10 racemic mixture of R-(+)-alpha lipoic acid and S-(-)-alpha lipoic acid. Preferably, as a 50/50 racemic mixture.

Advantageously, the binary or ternary formulation of the present invention contains R-(+)-alpha lipoic acid or a 50/50 or 60/40, 70/30, 80/20 or 90/10 racemic mixture of R-(+)-alpha lipoic acid and S-(-)-alpha lipoic acid in a microencapsulated or coated form (protected form for granules for sachets) or coated using a polymeric matrix (protected form for tablets) in the form of a non- dissociated acid or a salt, preferably a sodium salt. The formulation of the present invention, both in the form of tablets and of granules per sachets, must have a controlled and gradual release over time to ensure a level of lipoic acid in blood

serum from 0 to less than 4 hours. The formulation has a concentration comprised from 100 to 1200 milligrams/daily dose, even more preferably from 300 to 800 milligrams/daily dose.

In one embodiment, the formulation of the present invention, in the form of granules for sachets or hard capsules, consists of red yeast rice (*Monascus purpureus*) titrated in monacolin, for example it is titrated in monacolin at 3% or 5% or 10%; D-chiro inositol and/or myo-inositol and R-(+)-alpha lipoic acid or a 50/50 racemic mixture, the latter in a microencapsulated or coated form (alpha lipoic acid protected for granules or for tablets) with a controlled and gradual release over a period of from 0 to less than 4 hours.

The binary or ternary formulation of the present invention (pharmaceutical composition or nutraceutical composition or supplement product or food supplement) comprises a qualitative/quantitative chemical composition having the characteristics as set forth above, in combination with one or more excipients or additives, as described above. The formulation is prepared using apparatus and methods known to a person skilled in the art, who is undoubtedly capable of selecting the best operating conditions according to the type of formulation to be realized.
Initially, one proceeds to prepare a homogeneous and finely subdivided mixture. Said mixture will comprise red yeast rice (*Monascus purpureus*) titrated in monacolin, for example it is titrated in monacolin at 3% or 5% or 10%, D-chiro inositol and alpha lipoic acid and/or excipients and/or technological additives and/or co-formulants and/or polar and/or semipolar polymeric matrices and/or carriers and/or stabilizers according to the form of administration it is desired to prepare.

Said mixture is prepared by adding the various components in sequence inside a container equipped with stirring means and heating means.

It is also possible to use several types of matrices selected from among lipid matrices, carboxymethyl cellulose, carboxypropyl cellulose, hydroxypropyl cellulose and lacquer gum in order to formulate the composition in the desired form of administration.

Subsequently, using known apparatus and methods well known in the pharmaceutical and dietary supplements industry, a formulation is prepared in solid, granular or powder form, which is suitable for oral administration in the form of pills, tablets, softgels or orosoluble pharmaceutical forms.

The pharmaceutical composition or supplement product of the present invention (binary or ternary formulation) shows a surprisingly positive effect in the treated subjects.

The pharmaceutical composition or the supplement product of the present invention (binary or ternary formulation) can be administered once or twice a day for the purpose of administering to the subject undergoing treatment a daily dose as described above for each individual active component.

The pharmaceutical composition or supplement product of the present invention (binary or ternary formulation) can be administered both as a background therapy and a periodic therapy.

The Applicant tested the ternary formulation of the present invention by administering, twice a day, a 3 g sachet (granular ternary formulation) comprising:

- Red yeast rice (*Monascus purpureus*) titrated at 5%:
  150 mg;
- D-chiro inositol: 600 mg;
- Coated lipoic acid: 400 mg (weight of the lipoic acid prior to coating);
- Additives: approximately 1100 mg:
- Stabilizers: sorbitol, guar gum;
- Thickening agents: xanthan gum, maltodextrins;
- Acidifier: citric acid;
- Anti-agglomerant: silicon dioxide;
- Edulcorant: sucralose.

Two sachets per day were administered for a period comprised from 4 to 20 weeks. The ternary granular formulation of the present invention was tested in vivo on a group of 10 non-diabetic patients suffering from polycystic ovary syndrome (PCOS) in order to evaluate the effects of administering said ternary granular formulation on several specific parameters of the polycystic ovary syndrome. The control group was made up of 10 healthy subjects.

The 10 treated subjects (one 3 gram sachet per day) showed considerable improvements compared to the control group subjects who took a placebo.

The following parameters were evaluated and compared:

i) insulin sensitivity, based on insulinaemia,
ii) glucose tolerance, based on the HOMA and Quicki indexes,
iii) total cholesterol levels, via plasma assay,

iv) LDL cholesterol levels, via plasma assay,
v) HDL cholesterol levels, via plasma assay,
vi) triglyceride level, via plasma assay,
vii) CRP (C-reactive protein) values,
viii) Interleukin 1 (IL-1),
ix) TNF-alpha.

An unexpected lowering of triglycerides values, an increase in insulin sensitivity and a more marked reduction in total cholesterol and LDL were observed. Moreover, the tested formulation also improved some of the inflammatory parameters and risk factors mentioned above.

The Applicant also evaluated the administration of the ternary formulation on the lipid profile and degree of hirsutism in insulin resistant and hyperandrogenous women affected by PCOS.
The objective of the present study was to evaluate whether the administration of a ternary formulation of the present invention, in the form of a sachet containing a mixture consisting of: red yeast rice (*Monascus purpureus*) titrated at 5%: 150 mg; myo-inositol: 1000 mg and lipoic acid: 400 mg, was capable of reducing cholesterol levels and hyperandrogenous symptoms in insulin resistant women of fertile age with PCOS and an average degree of hirsutism (Ferriman-Gallwey > 8).
Materials and methods: an evaluation was performed on 30 women ranging in age from 20-30 years affected by micropolycystic ovary syndrome (PCOS), menstrual irregularity with an anovulatory cycle, HOMA > 2.5, BMI > 25 and hirsutism with a Ferriman-Gallwey score >8. The women were divided into 2 groups of 15:

- group A (15 women) were treated with the ternary formulation in sachets at a dose of 1 sachet per day for 6 months;

- group B (15 women) were treated with the ternary formulation in sachets at a dose of 2 sachets per day for 6 months.

All of the women underwent clinical evaluation prior to being enrolled and then 3 and 6 months after the beginning of the study in order to determine the degree of hirsutism based on the Ferriman-Gallwey score and an ultrasound scan to evaluate the dimensions of the ovaries and for an antral follicle count. Moreover, a baseline blood sample was taken from all of the women to determine the basal levels of insulin, glycaemia (HOMA index), cholesterol, HDL, LDL and triglycerides. Finally, the concentrations of LH, FSH, SHBG, E2, testosterone and free T were evaluated in all of the enrolled women.

The present study demonstrates that the results obtained from once-daily administration of the ternary formulation in the form of sachets are capable of improving the clinical picture and symptoms of the treated women (group A). Surprisingly, it was seen that unexpected results were obtained for the women belonging to group B.

## CLAIMS

1. A formulation comprising a mixture, wherein said mixture comprises or, alternatively, consists of the following compounds:

(i) a compound based on red yeast rice (*Monascus purpureus*) titrated in monacolin, and

(iii) a lipoic acid compound or a derivative thereof,

for use in:
(a) a preventive treatment of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome,

(b) a curative treatment for reducing and/or eliminating the symptoms of polycystic ovary syndrome and the metabolic disorders deriving from or connected to polycystic ovary syndrome.

2. The formulation for use in accordance with claim 1, for reducing the lipid profile and degree of hirsutism in insulin resistant and hyperandrogenous women affected by polycystic ovary syndrome –PCOS.

3. The formulation for use in accordance with claim 1 or 2, wherein said mixture comprises or, alternatively, consists of the following compounds:

(i) a compound based on red yeast rice (*Monascus purpureus*) titrated in monacolin,

(ii) a D-chiro-inositol and/or myo-inositol compound, and

(iii) a lipoic acid compound or a derivative thereof.

4. The formulation for use according to one of claims 1-3, wherein the red yeast rice (*Monascus purpureus*) titrated in monacolin has a monacolin titre comprised from 3% to 10% in monacolin.

5. The formulation for use according to one of claims 1-4, wherein said alpha lipoic acid is present as a 50/50 racemic R-(+)-alpha lipoic acid/S-(-)-alpha lipoic acid mixture

6. The formulation for use in accordance with any one of the preceding claims, wherein said acid alpha lipoic is present in microencapsulated or coated form.

7. The formulation for use in accordance with any one of the preceding claims, wherein said formulation is in solid form for oral administration, preferably tablets or granules for sachets or hard capsules.

8. The formulation for use in accordance with any one of the preceding claims as a pharmaceutical composition or supplement product.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000257

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/047 A61K31/366 A61K36/062 A61P3/00 A61P5/24
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, INSPEC, BEILSTEIN Data, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 2012/080831 A1 (LABOREST ITALIA S P A [IT]; AMELOTTI LUIGI [IT]; SECONDINI LORENZO [IT) 21 June 2012 (2012-06-21) the whole document page 5; claims; examples | 1-8 |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 June 2014 | 23/06/2014 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Orlando, Michele |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000257

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Information on patent family members

International application No
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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