



(51) International Patent Classification:

A61K 9/06 (2006.01) A61P 17/00 (2006.01)
A61K 47/10 (2017.01) A61P 17/06 (2006.01)
A61K 35/745 (2015.01) A61P 25/00 (2006.01)
A61K 35/747 (2015.01) A61P 25/16 (2006.01)
A61K 31/365 (2006.01) A61P 25/28 (2006.01)
A61K 31/4045 (2006.01) A61P 27/02 (2006.01)
A61K 31/4375 (2006.01) A61P 29/00 (2006.01)
A61K 31/4741 (2006.01) A61P 31/00 (2006.01)
A61K 31/4748 (2006.01) A61P 31/04 (2006.01)
A61K 31/7048 (2006.01) A61P 31/12 (2006.01)
A61P 9/10 (2006.01) A61P 35/00 (2006.01)
A61P 9/12 (2006.01) A61P 37/02 (2006.01)
A61P 11/00 (2006.01) A61P 37/08 (2006.01)
A61P 11/06 (2006.01) A61P 39/06 (2006.01)

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description (Rules 13bis.4(d)(i) and 48.2(a)(viii))

(21) International Application Number:

PCT/IB2017/053206

(22) International Filing Date:

31 May 2017 (31.05.2017)

(25) Filing Language:

Italian

(26) Publication Language:

English

(30) Priority Data:

102016000057122 01 June 2016 (01.06.2016) IT

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR,
KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: BACTERIA-BASED GEL COMPOSITIONS FOR TOPICAL APPLICATIONS AND USES THEREOF

(57) Abstract: The present invention relates to a composition for use as a medicament, in the form of a gel with characteristics of a reversible thermogel, based on one or more poloxamers, water and optionally excipients, and an effective amount of an active substance. Furthermore, the present invention relates to a process for the preparation of said composition and uses thereof.



WO 2017/208172 A1

"BACTERIA-BASED GEL COMPOSITIONS FOR TOPICAL APPLICATIONS AND USES THEREOF"

The present invention relates to a composition for use as a medicament, in the form of a gel with characteristics of a reversible thermogel, based on one or more poloxamers, water and optionally excipients, and an effective amount of an active substance. Furthermore, the present invention relates to a process for the preparation of said composition and uses thereof.

In the market, there exist various forms of administration of active ingredients, e.g. microorganisms such as bacteria, at least one flavonoid such as rutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents and/or arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, or rutoxides, as such or in the form of plant extracts containing said compounds, or melatonin or derivatives thereof. The topical forms of administration can be patches, creams, gels or suspensions. An example of a gel composition is described in EP2520279 A1.

However, there continues to be a felt need to be able to have a form of administration for topical use for transdermal application that is economical and easy to prepare, stable, efficacious in dosing the effective amount of active substance contained therein, and easily absorbable at the level of the cutis, dermis and epidermis without leaving residues or streaks.

The Applicant has developed a composition in gel form for topical use which provides an adequate and advantageous response to the above-mentioned needs.

The present invention relates to a composition in the form of gel for topical use, having the features as claimed in the accompanying claims.

The present invention relates to a process for the preparation of said composition, having the features as claimed in the accompanying claims.

The present invention relates to a composition for use as a medicament in gel form for topical use, having the features as claimed in the accompanying claims.

The preferred embodiments of the present invention set forth in the description that follows are illustrated solely by way of example and in no way limit the broad scope of application of the present invention, which will appear clear to the person skilled in the art.

In the context of the present invention, composition(s) means a pharmaceutical composition, a composition for medical devices, a composition for dietary supplements or a food composition.

Advantageously, the composition of the present invention is capable of releasing the active substance or active ingredient over time, in a constant, gradual and lasting manner as a controlled transdermal release, in such a way as to prolong its activity and therapeutic effectiveness over time.

Advantageously, the composition of the present invention is a gel in the form of a reversible thermogel thanks to the presence of a vehicle or carrier which contains specific selected polymers of the poloxamer type.

Advantageously, the composition of the present invention is for topical use for transdermal and/or transmucosal application, said composition is furthermore economical and easy to prepare, stable, efficacious in dosing the effective amount of active substance contained therein over time, and easily absorbable at the level of the cutis, dermis and epidermis without leaving residues or streaks.

The present invention relates to a composition (abbreviated as CMP) in the form of a gel for topical use. Said composition comprises:

- an effective amount of an active substance selected from the group comprising or, alternatively, consisting of:

- (i) at least one microorganism selected from the group comprising or, alternatively, consisting of: live lactic bacteria, live bifidobacteria, biologically active bacteria or active bacterial components, extracts or cell components, bacterial enzymes, tyndallized bacteria, lysed bacteria, sonicated bacteria and peptidoglycans; and

- (ii) melatonin and/or the natural and/or synthetic derivatives thereof;

preferably (iii) at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs and a vehicle or carrier, wherein said composition comprises or, alternatively, consists of an effective amount of a microorganism (i) selected from the group comprising or, alternatively, consisting of the microorganisms in Table 1; preferably said at least one microorganism is selected from the group comprising or, alternatively, consisting of the strains: *Lactobacillus salivarius* (LS01) DSM 22775, deposited on 23.07.2009; *Bifidobacterium breve* (BR03) DSM 16604, deposited on 20.07.2004; *Lactobacillus pentosus* (LPS01) DSM 21980, deposited on 14.11.2008; *Streptococcus thermophilus* (FP4) DSM 18616, deposited on 13.09.2006; *Lactobacillus casei ssp. rhamnosus* (LR04) DSM 16605, deposited on 20.07.2004; and *Lactobacillus acidophilus* (LA02) DSM 21717, deposited on 06.08.2008; even more preferably the strain is *Lactobacillus salivarius* (LS01) DSM 22775, and/or *Bifidobacterium breve* (BR03) DSM 16604, and/or *L. pentosus* (LPS01) DSM 21980, and wherein said composition is for topical transdermal use in the preventive and/or curative treatment of pathologies, disorders or diseases associated with/deriving from alterations of the immune system selected from the group comprising allergies, atopy, allergic rhinitis, food hypersensitivity, dermatitis, atopic dermatitis, eczema, psoriasis, asthma and immunodeficiencies. Said vehicle or carrier comprises water, preferably purified water, until reaching 100% by weight of the composition, and a thickening viscous matrix. Said thickening viscous matrix comprises or, alternatively, consists of at least one poloxamer or a mixture of poloxamers and, optionally, additives and/or excipients and/or adjuvants. Said additives and/or excipients and/or adjuvants are selected from among those capable of promoting the formation and stabilisation of the gel (reversible thermogel) and are selected from the group

comprising or, alternatively, consisting of acid salts, sodium sorbate, potassium sorbate, sodium benzoate, potassium benzoate, glycols, ethylene glycol and propylene glycol.

In a preferred embodiment (CMP1), the composition of the present invention (CMP) comprises a poloxamer which is selected from the group comprising or, alternatively, consisting of Poloxamer 124 CAS N. 9003-11-6 with an average molecular weight of 2090-2360, Poloxamer 188 (Lutrol F66) CAS No. 9003-11-6 with an average molecular weight of 7680-9510, Poloxamer 237 CAS N. 9003-11-6 with an average molecular weight of 6840-8830, Poloxamer 338 CAS N 9003-11-6 with an average molecular weight of 12700-17400, Poloxamer 407 (Lutrol® F127 Prill) CAS No. 9003-11-6 with an average molecular weight of 9840-14600, or mixtures thereof; preferably said Poloxamer 188 is present in an amount comprised from 0.1% to 10% by weight, out of 100 g of composition, preferably in an amount comprised from 0.5% to 5% by weight, for example from 1% to 3% by weight; and/or preferably said Poloxamer 407 is present in an amount comprised from 1% to 40% by weight, out of 100 g of composition, preferably in an amount comprised from 5% to 30% by weight, for example from 10% to 20% by weight (composition CMP1). Advantageously, the composition CMP1 contains Poloxamer 188 (Lutrol F66) CAS No. 9003-11-6 with an average molecular weight of 7680-9510 and/or Poloxamer 407 (Lutrol F127 Prill) CAS No. 900-11-6 with an average molecular weight of 984014600.

In another preferred embodiment (CMP4), the composition CMP or CMP1 comprises said microorganisms at a concentration comprised from 1×10^6 CFU/g to 1×10^{12} CFU/g of composition, preferably from 1×10^7 CFU/g to 1×10^{11} CFU/g of composition, even more preferably from 1×10^8 CFU/g to 1×10^{10} CFU/g of composition, for example 1×10^9 CFU/g of composition, and wherein:

- said microorganisms are present in said composition in an amount by weight comprised from 0.1% to 5%, preferably in an amount by weight comprised from 0.5% to 3%, even more preferably in an amount by weight comprised from 1% to 2%, relative to the total weight of the composition (CMP4).

In another preferred embodiment (CMP5), the composition CMP, CMP1 or 4 comprises an effective amount of an active substance selected from:

(iii) at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs; and

(ii) melatonin and/or the natural and/or synthetic derivatives thereof;

said active substance being present in said composition in an amount by weight comprised from 0.1% to 10% by weight, preferably in an amount comprised from 0.5% to 5% by weight, even more preferably from 1% to 3% by weight, relative to the total weight of the composition (CMP5).

In another embodiment (CMP6), the composition as described above is for use:

- in the treatment of pathologies, disorders or diseases due to the pathological malfunctioning of physiological functions connected with circadian rhythms;
- in the treatment of pathologies, disorders or diseases due to an abnormal or excessively high or excessively low blood pressure;
- in the treatment of pathologies, disorders or diseases due to an excess of free radicals and oxidative stress;
- in the treatment of pathologies, disorders or diseases due to an imbalance of the immune system;
- in the treatment of pathologies, disorders or diseases due to inflammatory states;
- in the treatment of pathologies, disorders or diseases due to acquired immunodeficiency;
- in the treatment of pathologies, disorders or diseases due to viral infections and bacterial infections;
- in a treatment as a support or adjuvant to chemotherapy;
- in the treatment of cancer with chemotherapeutic agents;
- in the treatment of sleep disorders in order to favour, in the treated subjects, the quality of sleep and regularity of sleep, with particular reference to REM sleep;
- in the treatment of pathologies, disorders or diseases of the eyes, of the retina, of the iris, of the optic nerve, retinal detachment and macular degeneration;
- in the treatment of vision disorders, in particular in maculopathy of the retina, via external applications in the vicinity of the eye and the temple;
- in the treatment of pathologies, disorders or diseases due to autism and Down's syndrome, in particular in children and adolescents, by favouring balance and control also of states of anxiety;
- in the treatment of pathologies, disorders or diseases due to senile dementia or Alzheimer's disease;
- in the treatment of pathologies, disorders or diseases due to Parkinson's disease or neurological dysfunctions, by improving sleep and tremors;
- in the treatment of pathologies, disorders or diseases due to pulmonary cystic fibrosis in children, by performing an anti-inflammatory activity;
- in the treatment of prostate tumours, by preventing the propagation thereof;
- in the treatment of tumours, as an anti-inflammatory, anti-tumour adjuvant;
- in the treatment of pathologies, disorders or diseases due to heart attack, myocardial infarction, cardiopathies, cardiac or coronary failure or myocardial insufficiency.

The present invention relates to a process for the preparation of a composition in accordance with the compositions CMP or CMP1 or 4 or 5 or 6, said process comprising the following steps:

- mixing in water, under continuous stirring, the various components, added in succession one after the other or separately premixed and added together, using a mixer provided with a temperature control and adjustment means and a stirring means, wherein the temperature is set at values lower than room temperature, comprised from 2°C to 16°C, preferably from 4°C to 10°C, for example from 6°C to 8°C, for a time comprised from 1 minute to 15 minutes so as to obtain a homogeneous mixture;

- maintaining said homogeneous mixture, preferably under continuous stirring, at a temperature comprised from 2°C to 10°C, preferably at a temperature comprised from 4°C to 8°C, for example from 5°C to 7°C, for a time comprised from 1 minute to 60 minutes, preferably from 5 minutes to 40 minutes, even more preferably from 10 minutes to 20 minutes, so as to obtain said composition in a liquid state;
- packaging said composition in sealed containers.

The vehicle present in the composition of the present invention comprises water and a thickening viscous matrix comprising at least one poloxamer or a mixture of at least due poloxamers.

In the context of the present invention, the term "*reversible thermogel*" refers to a gel obtained from aqueous copolymer solutions, wherein the copolymer is a poloxamer, capable of gelling in a reversible manner according to the temperature.

Typically, the composition, i.e. the reversible thermogel, of the present invention is liquid at temperatures below room temperature and becomes gelatinous at temperatures close to human body temperature. For example, said composition is liquid at temperatures approximately comprised from 3°C to 15°C; in particular, at about 5°C. Said composition in turn gels, that is, becomes a gel, starting from about 20°C until about 37°; in particular it gels between about 20° and 25°C, preferably, between about 21° and 23°C.

In the context of the present invention, the active agent, for example the melatonin, is present in the composition of the invention in an amount comprised from 0.1% to 3% by weight, out of 100 g of composition; preferably, comprised from 0.5% to 2% by weight, out of 100 g of composition; more preferably, about 1% by weight, out of 100 g of composition; even more preferably, 1% by weight, out of 100 g of composition. The melatonin can be added into the composition as such, in powder, with a purity comprised from 96% to 99.9%; in particular, with a purity comprised from 97% to 99%; for example, with a purity of the 98%. Alternatively, the melatonin can be added into the composition also in the form of microparticles, for example of a size comprised from 50 to 100 µm.

In the context of the present invention, the poloxamers are a series of block copolymers of ethylene oxide and propylene oxide in accordance with the following structural formula:



where *a* and *b* are whole numbers expressing the number of the oxyethylene and oxypropylene residues present in the molecule. Poloxamers are non-ionic copolymers of polyoxyethylene-polyoxypropylene used primarily in pharmaceutical formulations as emulsifying, solubilising or wetting agents.

The poloxamers of the present invention are capable of thickening the aqueous solutions and giving rise to reversible thermogels possessing rheological properties that vary according to their concentration and molecular weight. A large number of poloxamers (whose molecular weight varies widely according to the values of *a* and *b*) can be used for the purposes of the present invention. Among them, the five poloxamers (characterised by the codes 124, 188, 237, 338, 407, respectively) included in the US Pharmacopeia USP NF XVII, in the chapter headed "*Poloxamer*", whose contents are incorporated herein in their entirety, have proven to be preferable. Among these, the poloxamers are preferably

selected from the group consisting of Poloxamer 188 (Lutrol® F 68, BASF SE, Ludwigshafen, DE), CAS 9003-11-6; Poloxamer 407 (Lutrol® F 127, BASF SE, Ludwigshafen, DE), CAS 900-11-6; or mixtures thereof. In a preferred embodiment of the invention, a mixture of Poloxamer 188 and Poloxamer 407 is used.

In the context of the present invention, the at least one poloxamer or mixture of poloxamers is present in a total amount comprised from 1% to 35% by weight, out of 100 g of composition.

In a preferred embodiment of the invention,

the Poloxamer 188 is present in an amount comprised from 1% to 5% by weight, out of 100 g of composition; preferably, comprised from 1% to 3% by weight, out of 100 g of composition; more preferably, comprised from 1% to 2% by weight, out of 100 g of composition; even more preferably, of 1% by weight, out of 100 g of composition; and

the Poloxamer 407 is present in an amount comprised from 15% to 30% by weight, out of 100 g of composition; preferably, comprised from 18% to 25% by weight, out of 100 g of composition; more preferably, comprised from 20% to 23% by weight, out of 100 g of composition; even more preferably, of 21% by weight, out of 100 g of composition.

In the context of the present invention, the water is preferably purified water and is present in an amount such as to reach a balance at 100% by weight of the composition.

The composition of the present invention further comprises known additives/excipients/adjuvants commonly used in the pharmaceutical formulation technique; in particular, said additives/excipients/adjuvants are selected from among those particularly advantageous for the formation and the stabilisation of the reversible thermogel of the invention. In a preferred embodiment of the invention, said additives/excipients/adjuvants are selected from the group consisting of acid salts, such as sodium sorbate, potassium sorbate, sodium benzoate, potassium benzoate; and glycols, such as ethylene glycol and propylene glycol.

In a particularly preferred embodiment, said additives/excipients/adjuvants consist of potassium sorbate, sodium benzoate and propylene glycol, in a total amount comprised from 1 to 5% by weight, out of 100 g of composition.

The pharmaceutical composition for topical use in the form of a reversible thermogel of the present invention can be prepared by adopting well-known apparatus and processing conditions commonly used in the industry for the preparation of a reversible thermogel.

Essentially, the various ingredients making up the desired composition, added in succession or pre-mixed, undergo cold mixing using a suitable mixer provided with a refrigeration temperature control and adjustment means and a stirring means. The mixing temperature is set on values below room temperature, preferably between 3° and 8°C, and the mixture of components is kept under cold stirring for an amount of time sufficient to obtain a completely homogeneous mixture which, in an amount of time that will vary depending on the type of poloxamers used, will transform, still cold, into a completely liquid solution.

The product thus obtained is then packaged in suitable containers, e.g. sealed tubes, and subsequently, on reaching room temperature, will transform into a gel, in particular at the moment when it is applied on the skin.

In one embodiment (FR1), the present invention relates to a composition in the form of a gel for topical use comprising:

- an effective amount of an active substance selected from the group comprising or, alternatively, consisting of:

- (i) at least one microorganism selected from the group comprising or, alternatively, consisting of: live lactic bacteria, live bifidobacteria, biologically active bacteria or active bacterial components, cellular extracts or components, bacterial enzymes, tyndallized bacteria, lysed bacteria, sonicated bacteria and peptidoglycans; and/or

- (ii) at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs; and/or

- (iii) melatonin and/or the natural and/or synthetic derivatives thereof; and

- a vehicle or carrier comprising water, a thickening viscous matrix comprising or, alternatively, consisting of at least one poloxamer or a mixture of poloxamers and, optionally, additives and/or excipients and/or adjuvants selected from among those capable of promoting the formation and stabilisation of the gel, selected from the group comprising or, alternatively, consisting of acid salts, sodium sorbate, potassium sorbate, sodium benzoate, potassium benzoate, glycols, ethylene glycol and propylene glycol;

said composition being for use as a medicament.

In a preferred embodiment (FR2), the present invention relates to the composition for use according to FR1, wherein said poloxamer is selected from the group comprising or, alternatively, consisting of Poloxamer 124 with an average molecular weight of 2090-2360, Poloxamer 188 (Lutrol F66) CAS No. 9003-11-6 with an average molecular weight of 7680-9510, Poloxamer 237 with an average molecular weight of 6840-8830, Poloxamer 338 with an average molecular weight of 12700-17400, Poloxamer 407 (Lutrol F127 Prill) CAS No. 900-11-6, with an average molecular weight of 984014600, or mixtures thereof; preferably said Poloxamer 188 is present in an amount comprised from 0.1% to 10% by weight, out of 100g of composition, preferably in an amount comprised from 0.5% to 5% by weight, for example from 1% to 3% by weight; and/or preferably said Poloxamer 407 is present in an amount comprised from 1% to 40% by weight, out of 100g of composition, preferably in an amount comprised from 5% to 30% by weight, for example from 10% to 20% by weight.

In a preferred embodiment (FR3), the present invention relates to the composition for use according to FR1, wherein:

- said composition comprises or, alternatively, consists of an effective amount of an active substance selected from at least one microorganism (i) and, wherein:

- said composition is for topical transdermal use in the preventive and/or curative treatment of pathologies, disorders or diseases associated with/deriving from alterations of the immune system selected from the group comprising allergies, atopy, allergic rhinitis, food hypersensitivity, dermatitis, atopic dermatitis, eczema, psoriasis, asthma and immunodeficiencies.

In a preferred embodiment (FR4), the present invention relates to the composition for use according to one of FR1-FR3, wherein said at least one microorganism is selected from the group comprising or, alternatively, consisting of the microorganisms in Table 1; preferably said at least one microorganism is selected from the group comprising or, alternatively, consisting of the strains: *Lactobacillus salivarius* (LS01) DSM 22775, deposited on 23.07.2009; *Bifidobacterium breve* (BR03) DSM 16604, deposited on 20.07.2004; *Lactobacillus pentosus* (LPS01) DSM 21980, deposited on 14.11.2008; *Streptococcus thermophilus* (FP4) DSM 18616, deposited on 13.09.2006; *Lactobacillus casei ssp. rhamnosus* (LR04) DSM 16605, deposited on 20.07.2004; and *Lactobacillus acidophilus* (LA02) DSM 21717, deposited on 06.08.2008; even more preferably the strain is *Lactobacillus salivarius* (LS01) DSM 22775, and/or *Bifidobacterium breve* (BR03) DSM 16604, and/or *L. pentosus* (LPS01) DSM 21980.

In a preferred embodiment (FR5), the present invention relates to the composition for use according to FR4, wherein said microorganisms are present at a concentration comprised from 1×10^6 CFU/g to 1×10^{12} CFU/g of composition, preferably from 1×10^7 CFU/g to 1×10^{11} CFU/g of composition, even more preferably from 1×10^8 CFU/g to 1×10^{10} CFU/g of composition, for example 1×10^9 CFU/g of composition, and wherein:

- said microorganisms are present in said composition in an amount by weight comprised from 0.1% to 5%, preferably in an amount by weight comprised from 0.5% to 3%, even more preferably in an amount by weight comprised from 1% to 2%, relative to the total weight of composition.

In a preferred embodiment (FR6), the present invention relates to the composition for use according to FR1 or the FR2, wherein:

- said composition comprises or, alternatively, consists of an effective amount of an active substance selected from:

(ii) at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs; and/or

(iii) melatonin and/or the natural and/or synthetic derivatives thereof;

said active substance being present in said composition in an amount by weight comprised from 0.1% to 10% by weight, preferably in an amount comprised from 0.5% to 5% by weight, even more preferably from 1% to 3% by weight, relative to the total weight of the composition.

In a preferred embodiment (FR7), the present invention relates to the composition for use according to one of FR1- FR6, for use:

- in the treatment of pathologies, disorders or diseases due to the pathological malfunctioning of physiological functions connected with circadian rhythms;
- in the treatment of pathologies, disorders or diseases due to an abnormal or excessively high or excessively low blood pressure;
- in the treatment of pathologies, disorders or diseases due to an excess of free radicals and oxidative stress;
- in the treatment of pathologies, disorders or diseases due to an imbalance of the immune system;
- in the treatment of pathologies, disorders or diseases due to inflammatory states;
- in the treatment of pathologies, disorders or diseases due to acquired immunodeficiency;
- in the treatment of pathologies, disorders or diseases due to viral infections and bacterial infections;
- in a treatment as a support or adjuvant to chemotherapy;
- in the treatment of cancer with chemotherapeutic agents;
- in the treatment of sleep disorders in order to favour, in the treated subjects, the quality of sleep and regularity of sleep, with particular reference to REM sleep;
- in the treatment of pathologies, disorders or diseases of the eyes, of the retina, of the iris, of the optic nerve, retinal detachment and macular degeneration;
- in the treatment of vision disorders, in particular in maculopathy of the retina, via external applications in the vicinity of the eye and the temple;
- in the treatment of pathologies, disorders or diseases due to autism and Down's syndrome, in particular in children and adolescents, by favouring balance and control also of states of anxiety;
- in the treatment of pathologies, disorders or diseases due to senile dementia or Alzheimer's disease;
- in the treatment of pathologies, disorders or diseases due to Parkinson's disease or neurological dysfunctions, by improving sleep and tremors;
- in the treatment of pathologies, disorders or diseases due to pulmonary cystic fibrosis in children, by performing an anti-inflammatory activity;
- in the treatment of prostate tumours, by preventing the propagation thereof;
- in the treatment of tumours, as an anti-inflammatory, anti-tumour adjuvant;
- in the treatment of pathologies, disorders or diseases due to heart attack, myocardial infarction, cardiopathies, cardiac or coronary failure or myocardial insufficiency.

In a preferred embodiment (FR8), the present invention relates to a process for the preparation of a composition in accordance with any one of FR1 – FR7, said process comprising the following steps:

- mixing in water, under continuous stirring, the various components, added in succession one after the other or separately premixed and added together, using a mixer provided with a temperature control and adjustment means and a stirring means, wherein the temperature is set at values lower than room temperature, comprised from 2°C to 16°C, preferably from 4°C to 10°C, for example from 6°C to 8°C, for a time comprised from 1 minute to 15 minutes so as to obtain a homogeneous mixture;
- maintaining said homogeneous mixture, preferably under continuous stirring, at a temperature comprised from 2°C to 10°C, preferably at a temperature comprised from 4°C to 8°C, for example from 5°C to 7°C, for a time comprised from 1 minute to 60 minutes, preferably from 5 minutes to 40 minutes, even more preferably from 10 minutes to 20 minutes, so as to obtain said composition in a liquid state;
- packaging said composition in sealed containers.

Solely by way of example, which does not limit the various possibilities of production, an example of preparation of a reversible thermogel/composition of the present invention is described here below.

Example 1 – Preparation of a lot of a composition (in the form of a reversible thermogel) of the present invention

Component	weight (g)	%
Mixture of bacteria (1) or (2) or (3) or (4) or (5)	2.00	1.00
Poloxamer 188	4.00	2.00
Poloxamer 407	40.00	20.00
K sorbate	0.40	0.20
Na benzoate	1.00	0.50
Propylene glycol	2.00	1.00
Purified water	150.60	75.30
TOTAL	200.00	100.00

Mixture (1) consisting of only *Lactobacillus salivarius* (LS01) DSM 22775, or only *Bifidobacterium breve* (BR03) DSM 16604, or only *L. pentosus* (LPS01) DSM 21980.

Mixture (2) consisting of *Lactobacillus salivarius* (LS01) DSM 22775, *Bifidobacterium breve* (BR03) DSM 16604 and *L. pentosus* (LPS01) DSM 21980, in a ratio by weight of 1:1:1.

Mixture (3) consisting of *Lactobacillus salivarius* (LS01) DSM 22775 and *Bifidobacterium breve* (BR03) DSM 16604 in a ratio by weight of 1:1.

Mixture (4) consisting of *Lactobacillus salivarius* (LS01) DSM 22775 and *L. pentosus* (LPS01) DSM 21980, in a ratio by weight of 1:1.

Mixture (5) consisting of *Bifidobacterium breve* (BR03) DSM 16604 and *L. pentosus* (LPS01) DSM 21980, in a ratio by weight of 1:1.

The cold purified water (at 5°C) is weighed into a glass container (for example a beaker) with magnetic stirring, a thermometer, and an external ice bath and the potassium sorbate and sodium benzoate are

added under stirring. The mixture is maintained under stirring at 5°C until complete dissolution of the salts. Then the following are added, again under stirring: the two poloxamers (crystalline), in succession or in a mixture, the methionine (in powder, or in the form of micro-/nanoparticles) and the propylene glycol and cold stirring is continued for at least 15 minutes until a homogeneous appearance is obtained. The container is then placed in a refrigerator at 5°C for at least 24 h, until obtaining complete dissolution of the ingredients.

After this, the resulting product (liquid) is packaged in 18-20 g tubes and sealed pending use/experimentation. On reaching room temperature and in contact with the skin the product transforms completely into a gel, which is rapidly absorbed following cutaneous and/or transmucosal administration. The pH of the liquid thermogel is 7.40. The gelling temperature is 21°-22°C.

The composition in the form of a thermogel of the present invention, topically administered, in particular on wrists and/or forearms, has shown an excellent cutaneous permeability, triggering a fast onset of the pharmacological action. Furthermore, thanks to the fact of going directly into circulation without passing through the gastrointestinal tract (no metabolism by the liver), it has also shown high blood levels of the active ingredient, for example, melatonin, for a prolonged period of time (slow release). This fact has made it possible to apply low dosages of the drug, thus obtaining the desired advantageous results (modest dosage/high, long-lasting activity) compared to the traditional forms of administration thereof.

For example, a study was conducted on 10 healthy volunteers with different formulations of melatonin, observing the accumulation of melatonin in the saliva over time (it is well known that melatonin spreads passively into saliva via the bloodstream, and its concentration therein represents 24%-33% of its plasma levels, that is to say, the amount of free melatonin not bound to globulins).

The following treatments were administered to the volunteers, randomly divided into 3 groups:

1. treatment with a formulation of melatonin in a reversible thermogel in accordance with the present invention (dosage 1 mg/g, single dose)
2. treatment with a formulation of melatonin in a reversible thermogel in accordance with the present invention (dosage 2 mg/g, single dose)
3. treatment with a formulation of melatonin in cream (dosage 1 mg/g, single dose)
4. treatment with melatonin in tablets (dosage 1 mg/tablet).

A saliva sample was taken at time 0 (basal) and at subsequent times (up to 7 h) after administration, using a Cortisol-Salivette® device (SARSTEDT S.r.l., Verona, IT); the melatonin levels in the saliva were determined by LC-MS (liquid chromatography – mass spectrometry) using a triple quadrupole mass spectrometer (ABSciex QTrap 3200) and substantially following the method of Khan et al. 2013.

The study showed that the formulations of melatonin in a reversible thermogel in accordance with the present invention possess an excellent thermal permeability, a fast onset of the pharmacological action and a lasting duration thereof compared to the other formulations tested.

The pharmaceutical compositions of the present invention also showed to act effectively on all of the patients treated, whereas the commonly used formulations, such as, for example, oral ones, do not act on all individuals.

Furthermore, the pharmaceutical compositions of the present invention have also shown to possess good stability over time.

The pharmaceutical compositions of the present invention are particularly recommended both for transdermal administration and transmucosal administration.

The pharmaceutical compositions of the present invention have shown to be advantageously active, or in any case very promising in the treatment of a number of disorders/diseases due to dysfunctions of physiological functions connected with circadian rhythms such as, for example, the sleep-wake balance; in the regulation of blood pressure; in eliminating of free radicals; in interacting with the immune system, for example, in the treatment of inflammatory states, in the treatment of acquired immunodeficiencies and in the treatment of viral and bacterial infectious diseases and cancer.

Furthermore, the compositions of the present invention have shown to be useful: in the treatment of sleep disorders in all the treated subjects, by favouring the quality of sleep, in particular of REM sleep; in the treatment of the autism and Down syndrome, particularly in children, by favouring their balance; in the treatment of Alzheimer's disease; in the treatment of Parkinson's disease, by improving sleep and tremors; in the treatment of the vision disorders, for example in maculopathy of the retina, via external applications in the vicinity of the eye; in the treatment of the pulmonary manifestations of cystic fibrosis in children, where they provide an anti-inflammatory action; in the treatment of prostate cancer, where they are capable of preventing the propagation thereof; in the treatment of the tumours, as anti-inflammatory, anti-tumour adjuvants.

No.	Name	Commercial code	Depository institution	Deposit number	Deposit date	Depositor
1	<i>Lactobacillus casei</i>	LF1i	CNCM I.P.	I-785	21.07.1988	Anidral Srl
2	<i>Lactobacillus gasseri</i>	LF2i	CNCM I.P.	I-786	21.07.1988	Anidral Srl
3	<i>Lactobacillus crispatus</i>	LF3i	CNCM I.P.	I-787	21.07.1988	Anidral Srl
4	<i>Lactobacillus fermentum</i>	LF4i	CNCM I.P.	I-788	21.07.1988	Anidral Srl
5	<i>Lactobacillus fermentum</i>	LF5	CNCM I.P.	I-789	21.07.1988	Anidral Srl
6	<i>Lactobacillus casei</i> ssp. <i>pseudoplanarum</i>	LFH i	CNCM I.P.	I-790	21.07.1988	Anidral Srl
7	<i>Streptococcus thermophilus</i> B39		BCCM LMG	LMG P-18383	5.05.1998	Anidral Srl
8	<i>Streptococcus thermophilus</i> T003		BCCM LMG	LMG P-18384	5.05.1998	Anidral Srl
9	<i>Lactobacillus pentosus</i> 9 /1 ei		BCCM LMG	LMG P-21019	16.10.2001	Mofin Srl
10	<i>Lactobacillus plantarum</i> 776 /1 bi	LP 02	BCCM LMG	LMG P-21020	16.10.2001	Mofin Srl
11	<i>Lactobacillus plantarum</i> 476LL 20 bi	LP 01	BCCM LMG	LMG P-21021	16.10.2001	Mofin Srl
12	<i>Lactobacillus plantarum</i> PR ci		BCCM LMG	LMG P-21022	16.10.2001	Mofin Srl
13	<i>Lactobacillus plantarum</i> 776 /2 hi		BCCM LMG	LMG P-21023	16.10.2001	Mofin Srl
14	<i>Lactobacillus casei</i> ssp. <i>paracasei</i> 181A/3 ai ai	LPC00	BCCM LMG	LMG P-21380	31.01.2002	Anidral Srl
15	<i>Lactobacillus</i> belonging to the <i>acidophilus</i> group 192A/1 ai ai	LA 02	BCCM LMG	LMG P-21381	31.01.2002	Anidral Srl
16	<i>Bifidobacterium longum</i> 175A/1 ai ai		BCCM LMG	LMG P-21382	31.01.2002	Anidral Srl

17	<i>Bifidobacterium breve</i> 195A/1 aici		BCCM LMG	LMG P-21383	31.01.2002	Anidral Srl
18	<i>Bifidobacterium lactis</i> 32A/3 aiai	BS 01	BCCM LMG	LMG P-21384	31.01.2002	Anidral Srl
19	<i>Lactobacillus plantarum</i> 501/2 gi	COAKTIV	BCCM LMG	LMG P-21385	31.01.2002	Mofin Srl
20	<i>Lactococcus lactis</i> ssp. <i>lactis</i> 501/4 ci		BCCM LMG	LMG P-21388	31.01.2002	Mofin Srl
21	<i>Lactococcus lactis</i> ssp. <i>lactis</i> 501/4 hi		BCCM LMG	LMG P-21387	15.03.2002	Mofin Srl
22	<i>Lactococcus lactis</i> ssp. <i>lactis</i> 501/4 ci		BCCM LMG	LMG P-21388	31.01.2002	Mofin Srl
23	<i>Lactobacillus plantarum</i> 501/4 li		BCCM LMG	LMG P-21389	15.03.2002	Mofin Srl
24	<i>Lactobacillus acidophilus</i>	LA08	BCCM LMG	LMG P-26144	03.11.2010	Probiotical SpA
25	<i>Lactobacillus paracasei</i> ssp. <i>paracasei</i>	LPC10	BCCM LMG	LMG P-26143	03.11.2010	Probiotical SpA
26	<i>Streptococcus thermophilus</i>	GB1	DSMZ	DSM 16506	18.06.2004	Anidral Srl
27	<i>Streptococcus thermophilus</i>	GB5	DSMZ	DSM 16507	18.06.2004	Anidral Srl
28	<i>Streptococcus thermophilus</i>	Y02	DSMZ	DSM 16590	20.07.2004	Anidral Srl
29	<i>Streptococcus thermophilus</i>	Y03	DSMZ	DSM 16591	20.07.2004	Anidral Srl
30	<i>Streptococcus thermophilus</i>	Y04	DSMZ	DSM 16592	20.07.2004	Anidral Srl
31	<i>Streptococcus thermophilus</i>	Y05	DSMZ	DSM 16593	20.07.2004	Anidral Srl
32	<i>Bifidobacterium adolescentis</i>	BA 03	DSMZ	DSM 16594	21.07.2004	Anidral Srl
=						
56						
33	<i>Bifidobacterium adolescentis</i>	BA 04	DSMZ	DSM 16595	21.07.2004	Anidral Srl

34	<i>Bifidobacterium breve</i>	BR 04	DSMZ	DSM 16596	21.07.2004	Anidral Srl
35	<i>Bifidobacterium pseudocatenulatum</i>	BP 01	DSMZ	DSM 16597	21.07.2004	Anidral Srl
36	<i>Bifidobacterium pseudocatenulatum</i>	BP 02	DSMZ	DSM 16598	21.07.2004	Anidral Srl
37	<i>Bifidobacterium longum</i>	BL 03	DSMZ	DSM 16603	20.07.2004	Anidral Srl
38	<i>Bifidobacterium breve</i>	BR 03	DSMZ	DSM 16604	20.07.2004	Anidral Srl
39	<i>Lactobacillus casei</i> ssp. <i>thermophilus</i>	LR 04	DSMZ	DSM 16605	20.07.2004	Anidral Srl
40	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i>	LDB 01	DSMZ	DSM 16606	20.07.2004	Anidral Srl
41	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i>	LDB 02	DSMZ	DSM 16607	20.07.2004	Anidral Srl
42	<i>Staphylococcus xylophilus</i>	SX 01	DSMZ	DSM 17102	01.02.2005	Anidral Srl
43	<i>Bifidobacterium adolescentis</i>	BA 02	DSMZ	DSM 17103	01.02.2005	Anidral Srl
= 57						
44	<i>Lactobacillus plantarum</i>	LP 07	DSMZ	DSM 17104	01.02.2005	Anidral Srl
45	<i>Streptococcus thermophilus</i>	YO8	DSMZ	DSM 17843	21.12.2005	Anidral Srl
46	<i>Streptococcus thermophilus</i>	YO9	DSMZ	DSM 17844	21.12.2005	Anidral Srl
47	<i>Streptococcus thermophilus</i>	YO100	DSMZ	DSM 17845	21.12.2005	Anidral Srl
48	<i>Lactobacillus fermentum</i>	LF06	DSMZ	DSM 18295	24.05.2006	Anidral Srl
49	<i>Lactobacillus fermentum</i>	LF07	DSMZ	DSM 18296	24.05.2006	Anidral Srl
50	<i>Lactobacillus fermentum</i>	LF08	DSMZ	DSM 18297	24.05.2006	Anidral Srl
51	<i>Lactobacillus fermentum</i>	LF09	DSMZ	DSM 18298	24.05.2006	Anidral Srl
52	<i>Lactobacillus gasseri</i>	LGS01	DSMZ	DSM 18299	24.05.2006	Anidral Srl
53	<i>Lactobacillus gasseri</i>	LGS02	DSMZ	DSM 18300	24.05.2006	Anidral Srl

54	<i>Lactobacillus gasseri</i>	LGS03	DSMZ	DSM 18301	24.05.2006	Anidral Srl
55	<i>Lactobacillus gasseri</i>	LGS04	DSMZ	DSM 18302	24.05.2006	Anidral Srl
56	<i>Bifidobacterium adolescentis</i> EI-3	BA 03	DSMZ	DSM 18350	15.06.2006	Anidral Srl
=	<i>Bifidobacterium catenulatum</i>					
32	<i>sp./pseudocatenulatum</i> EI-31, ID 09-255					
57	<i>Bifidobacterium adolescentis</i> EI-15	BA 02	DSMZ	DSM 18351	15.06.2006	Anidral Srl
= 43						
58	<i>Bifidobacterium adolescentis</i> EI-18	BA 05	DSMZ	DSM 18352	15.06.2006	Anidral Srl
	<i>Bifidobacterium animalis subsp. lactis</i> EI-18, ID 09-256					
59	<i>Bifidobacterium catenulatum</i> EI-20	BC 01	DSMZ	DSM 18353	15.06.2006	Anidral Srl
60	<i>Streptococcus thermophilus</i> FRai	MO1	DSMZ	DSM 18613	13.09.2006	Mofin Srl
61	<i>Streptococcus thermophilus</i> LB2bi	MO2	DSMZ	DSM 18614	13.09.2006	Mofin Srl
62	<i>Streptococcus thermophilus</i> LRci	MO3	DSMZ	DSM 18615	13.09.2006	Mofin Srl
63	<i>Streptococcus thermophilus</i> FP4	MO4	DSMZ	DSM 18616	13.09.2006	Mofin Srl
64	<i>Streptococcus thermophilus</i> ZZ5F8	MO5	DSMZ	DSM 18617	13.09.2006	Mofin Srl
65	<i>Streptococcus thermophilus</i> TEO4	MO6	DSMZ	DSM 18618	13.09.2006	Mofin Srl
66	<i>Streptococcus thermophilus</i> S1ci	MO7	DSMZ	DSM 18619	13.09.2006	Mofin Srl
67	<i>Streptococcus thermophilus</i> 641bi	MO8	DSMZ	DSM 18620	13.09.2006	Mofin Srl
68	<i>Streptococcus thermophilus</i> 277A/1ai	MO9	DSMZ	DSM 18621	13.09.2006	Mofin Srl
69	<i>Streptococcus thermophilus</i> 277A/2ai	MO10	DSMZ	DSM 18622	13.09.2006	Mofin Srl

70	<i>Streptococcus thermophilus</i> IDC11	MO11	DSMZ	DSM 18623	13.09.2006	Mofin Srl
71	<i>Streptococcus thermophilus</i> ML3di	MO14	DSMZ	DSM 18624	13.09.2006	Mofin Srl
72	<i>Streptococcus thermophilus</i> TEO3	MO15	DSMZ	DSM 18625	13.09.2006	Mofin Srl
73	<i>Streptococcus thermophilus</i> G62	GG1	DSMZ	DSM 19057	21.02.2007	Mofin Srl
74	<i>Streptococcus thermophilus</i> G1192	GG2	DSMZ	DSM 19058	21.02.2007	Mofin Srl
75	<i>Streptococcus thermophilus</i> GB18	GG3 MO2	DSMZ	DSM 19059	21.02.2007	Mofin Srl
76	<i>Streptococcus thermophilus</i> CCR21	GG4	DSMZ	DSM 19060	21.02.2007	Mofin Srl
77	<i>Streptococcus thermophilus</i> G92	GG5	DSMZ	DSM 19061	21.02.2007	Mofin Srl
78	<i>Streptococcus thermophilus</i> G69	GG6	DSMZ	DSM 19062	21.02.2007	Mofin Srl
79	<i>Streptococcus thermophilus</i>	YO 10	DSMZ	DSM 19063	21.02.2007	Anidral Srl
80	<i>Streptococcus thermophilus</i>	YO 11	DSMZ	DSM 19064	21.02.2007	Anidral Srl
81	<i>Streptococcus thermophilus</i>	YO 12	DSMZ	DSM 19065	21.02.2007	Anidral Srl
82	<i>Streptococcus thermophilus</i>	YO 13	DSMZ	DSM 19066	21.02.2007	Anidral Srl
83	<i>Weissella</i> ssp. WSP 01	EX	DSMZ	DSM 19067	21.02.2007	Anidral Srl
84	<i>Weissella</i> ssp. WSP 02	EX	DSMZ	DSM 19068	21.02.2007	Anidral Srl
85	<i>Lactobacillus</i> ssp. WSP 03	EX	DSMZ	DSM 19069	21.02.2007	Anidral Srl
86	<i>Lactobacillus plantarum</i> LP 09	OY	DSMZ	DSM 19070	21.02.2007	Anidral Srl
87	<i>Lactobacillus plantarum</i> LP 10	OY	DSMZ	DSM 19071	21.02.2007	Anidral Srl
88	<i>Lactococcus lactis</i>	NS 01	DSMZ	DSM 19072	21.02.2007	Anidral Srl
89	<i>Lactobacillus fermentum</i>	LF 10	DSMZ	DSM 19167	20.03.2007	Anidral Srl

90	<i>Lactobacillus fermentum</i>	LF 11	DSMZ	DSM 19188	20.03.2007	Anidral Srl
91	<i>Lactobacillus casei</i> ssp. <i>rhamnosus</i>	LR05	DSMZ	DSM 19739	27.09.2007	Anidral Srl
92	<i>Bifidobacterium bifidum</i>	BB01	DSMZ	DSM 19818	30.10.2007	Anidral Srl
93	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LD 01	Lb	DSMZ	DSM 19948	28.11.2007	Anidral Srl
94	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LD 02	Lb	DSMZ	DSM 19949	28.11.2007	Anidral Srl
95	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LD 03	Lb	DSMZ	DSM 19950	28.11.2007	Anidral Srl
96	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LD 04	Lb	DSMZ	DSM 19951	28.11.2007	Anidral Srl
97	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LD 05	Lb	DSMZ	DSM 19952	28.11.2007	Anidral Srl
98	<i>Bifidobacterium pseudocatenulatum</i>	B660	DSMZ	DSM 21444	13.05.2008	Probiotal SpA
99	<i>Lactobacillus acidophilus</i>	LA02	DSMZ	DSM 21717	06.08.2008	Probiotal SpA
100	<i>Lactobacillus paracasei</i>	LPC 08	DSMZ	DSM 21718	06.08.2008	Probiotal SpA
101	<i>Lactobacillus pentosus</i>	LPS 01	DSMZ	DSM 21980	14.11.2008	Probiotal SpA
102	<i>Lactobacillus rhamnosus</i>	LR 06	DSMZ	DSM 21981	14.11.2008	Probiotal

103	<i>Lactobacillus delbrueckii</i> ssp. <i>delbrueckii</i>	DSMZ 20074	DSMZ	DSM 22106	10.12.2008	Probiotal SpA
104	<i>Lactobacillus plantarum</i>	LP1	DSMZ	DSM 22107	10.12.2008	Probiotal SpA
105	<i>Lactobacillus salivarius</i>	LS01	DSMZ	DSM 22775	23.07.2009	Probiotal SpA
106	<i>Lactobacillus salivarius</i>	LS03	DSMZ	DSM 22776	23.07.2009	Probiotal SpA
107	<i>Bifidobacterium bifidum</i>	BB01	DSMZ	DSM 22892	28.08.2009	Probiotal SpA
108	<i>Bifidobacterium bifidum</i>		DSMZ	DSM 22893	28.08.2009	Probiotal SpA
109	<i>Bifidobacterium bifidum</i>	BB03	DSMZ	DSM 22894	28.08.2009	Probiotal SpA
110	<i>Bifidobacterium lactis</i>	BS05	DSMZ	DSM 23032	13.10.2009	Probiotal SpA
111	<i>Lactobacillus acidophilus</i>	LA 06	DSMZ	DSM 23033	13.10.2009	Probiotal SpA
112	<i>Lactobacillus brevis</i>	LBR01	DSMZ	DSM 23034	13.10.2009	Probiotal SpA
113	<i>Bifidobacterium animalis</i> ssp. <i>lactis</i>	BS06	DSMZ	DSM 23224	12.01.2010	Probiotal

114	<i>Bifidobacterium longum</i>	BL04	DSMZ	DSM 23233	12.01.2010	Probiotal SpA
115	<i>Bifidobacterium longum</i>	BL05	DSMZ	DSM 23234	12.01.2010	Probiotal SpA
116	<i>Bifidobacterium bifidum</i>	MB 109	DSMZ	DSM 23731	29.06.2010	Probiotal SpA
117	<i>Bifidobacterium breve</i>	MB 113	DSMZ	DSM 23732	29.06.2010	Probiotal SpA
118	<i>Bifidobacterium lactis</i>	MB 2409	DSMZ	DSM 23733	29.06.2010	Probiotal SpA
119	<i>Lactobacillus reuteri</i>	LRE01	DSMZ	DSM 23877	05.08.2010	Probiotal SpA
120	<i>Lactobacillus reuteri</i>	LRE02	DSMZ	DSM 23878	05.08.2010	Probiotal SpA
121	<i>Lactobacillus reuteri</i>	LRE03	DSMZ	DSM 23879	05.08.2010	Probiotal SpA
122	<i>Lactobacillus reuteri</i>	LRE04	DSMZ	DSM 23880	05.08.2010	Probiotal SpA
123	<i>Lactobacillus paracasei</i> ssp. <i>paracasei</i>	LPC09	DSMZ	DSM 24243	23.11.2010	Probiotal SpA
124	<i>Lactobacillus acidophilus</i>	LA 07	DSMZ	DSM 24303	23.11.2010	Probiotal

125	<i>Bifidobacterium bifidum</i>	BB04	DSMZ	DSM 24437	04.01.2011	Probiotal SpA
126	<i>Lactobacillus crispatus</i>	CRL 1251	DSMZ	DSM 24438	04.01.2011	Probiotal SpA
127	<i>Lactobacillus crispatus</i>	CRL 1266	DSMZ	DSM 24439	04.01.2011	Probiotal SpA
128	<i>Lactobacillus paracasei</i>	CRL 1289	DSMZ	DSM 24440	04.01.2011	Probiotal SpA
129	<i>Lactobacillus salivarius</i>	CRL 1328	DSMZ	DSM 24441	04.01.2011	Probiotal SpA
130	<i>Lactobacillus gasseri</i>	CRL 1259	DSMZ	DSM 24512	25.01.2011	Probiotal SpA
131	<i>Lactobacillus acidophilus</i>	CRL 1294	DSMZ	DSM 24513	25.01.2011	Probiotal SpA
132	<i>Lactobacillus salivarius</i>	LS04	DSMZ	DSM 24618	02.03.2011	Probiotal SpA
133	<i>Lactobacillus crispatus</i>	LCR01	DSMZ	DSM 24619	02.03.2011	Probiotal SpA
134	<i>Lactobacillus crispatus</i>	LCR02	DSMZ	DSM 24620	02.03.2011	Probiotal SpA
135	<i>Lactobacillus acidophilus</i>	LA09	DSMZ	DSM 24621	02.03.2011	Probiotal

136	<i>Lactobacillus gasseri</i>	LGS05	DSMZ	DSM 24622	02.03.2011	Probiotal SpA
137	<i>Lactobacillus paracasei</i>	LPC11	DSMZ	DSM 24623	02.03.2011	Probiotal SpA
138	<i>Bifidobacterium infantis</i>	BI 02	DSMZ	DSM 24687	29.03.2011	Probiotal SpA
139	<i>Bifidobacterium bifidum</i>	BB 06	DSMZ	DSM 24688	29.03.2011	Probiotal SpA
140	<i>Bifidobacterium longum</i>	BL 06	DSMZ	DSM 24689	29.03.2011	Probiotal SpA
141	<i>Bifidobacterium lactis</i>	BS 07	DSMZ	DSM 24690	29.03.2011	Probiotal SpA
142	<i>Bifidobacterium longum</i>	PCB133	DSMZ	DSM 24691	29.03.2011	Probiotal SpA
143	<i>Bifidobacterium breve</i>	B632	DSMZ	DSM 24706	07.04.2011	Probiotal SpA
144	<i>Bifidobacterium breve</i>	B2274	DSMZ	DSM 24707	07.04.2011	Probiotal SpA
145	<i>Bifidobacterium breve</i>	B7840	DSMZ	DSM 24708	07.04.2011	Probiotal SpA
146	<i>Bifidobacterium longum</i>	B1975	DSMZ	DSM 24709	07.04.2011	Probiotal

147	<i>Lactobacillus salivarius</i>	DLV1	DSMZ	DSM 25138	02.09.2011	Probiotal SpA
148	<i>Lactobacillus reuteri</i>	LRE05	DSMZ	DSM 25139	02.09.2011	Probiotal SpA
149	<i>Lactobacillus reuteri</i>	LRE06	DSMZ	DSM 25140	02.09.2011	Probiotal SpA
150	<i>Lactobacillus reuteri</i>	RC 14	DSMZ	DSM 25141	02.09.2011	Probiotal SpA
151	<i>Streptococcus thermophilus</i>	ST 10	DSMZ	DSM 25246	19.09.2011	Probiotal SpA
152	<i>Streptococcus thermophilus</i>	ST 11	DSMZ	DSM 25247	19.09.2011	Probiotal SpA
153	<i>Streptococcus thermophilus</i>	ST 12	DSMZ	DSM 25282	20.10.2011	Probiotal SpA
154	<i>Lactobacillus salivarius</i>	DLV8	DSMZ	DSM 25545	12.01.2012	Probiotal SpA
155	<i>Bifidobacterium longum</i>	DLBL 07	DSMZ	DSM 25669	16.02.2012	Probiotal SpA
156	<i>Bifidobacterium longum</i>	DLBL 08	DSMZ	DSM 25670	16.02.2012	Probiotal SpA
157	<i>Bifidobacterium longum</i>	DLBL 09	DSMZ	DSM 25671	16.02.2012	Probiotal

158	<i>Bifidobacterium longum</i>	DLBL 10	DSMZ	DSM 25672	16.02.2012	Probiotal SpA
159	<i>Bifidobacterium longum</i>	DLBL 11	DSMZ	DSM 25673	16.02.2012	Probiotal SpA
160	<i>Bifidobacterium longum</i>	DLBL 12	DSMZ	DSM 25674	16.02.2012	Probiotal SpA
161	<i>Bifidobacterium longum</i>	DLBL 13	DSMZ	DSM 25675	16.02.2012	Probiotal SpA
162	<i>Bifidobacterium longum</i>	DLBL 14	DSMZ	DSM 25676	16.02.2012	Probiotal SpA
163	<i>Bifidobacterium longum</i>	DLBL 15	DSMZ	DSM 25677	16.02.2012	Probiotal SpA
164	<i>Bifidobacterium longum</i>	DLBL 16	DSMZ	DSM 25678	16.02.2012	Probiotal SpA
165	<i>Bifidobacterium longum</i>	DLBL 17	DSMZ	DSM 25679	16.02.2012	Probiotal SpA
166	<i>Lactobacillus johnsonii</i>	DLLJO 01	DSMZ	DSM 25680	16.02.2012	Probiotal SpA
167	<i>Lactobacillus rhamnosus</i>	DLLR 07	DSMZ	DSM 25681	16.02.2012	Probiotal SpA
168	<i>Lactobacillus rhamnosus</i>	DLLR 08	DSMZ	DSM 25682	16.02.2012	Probiotal

169	<i>Lactobacillus reuteri</i>	DLLRE 07	DSMZ	DSM 25683	16.02.2012	Probiological SpA
170	<i>Lactobacillus reuteri</i>	DLLRE 08	DSMZ	DSM 25684	16.02.2012	Probiological SpA
171	<i>Lactobacillus reuteri</i>	DLLRE 09	DSMZ	DSM 25685	16.02.2012	Probiological SpA
172	<i>Bifidobacterium longum</i>	DLBL 18	DSMZ	DSM 25708	24.02.2012	Probiological SpA
173	<i>Bifidobacterium infantis</i>	BI 03	DSMZ	DSM 25709	24.02.2012	Probiological SpA
174	<i>Lactobacillus plantarum</i>	LP 09	DSMZ	DSM 25710	24.02.2012	Probiological SpA
175	<i>Bifidobacterium longum</i>	DLBL 19	DSMZ	DSM 25717	01.03.2012	Probiological SpA
176	<i>Bifidobacterium longum</i>	DLBL 20	DSMZ	DSM 25718	01.03.2012	Probiological SpA
177	<i>Lactobacillus salivarius</i>	LS 05	DSMZ	DSM 26036	06.06.2012	Probiological SpA
178	<i>Lactobacillus salivarius</i>	LS 06	DSMZ	DSM 26037	06.06.2012	Probiological SpA
179	<i>Lactobacillus pentosus</i>	LPS 02	DSMZ	DSM 26038	06.06.2012	Probiological

180	<i>Bifidobacterium pseudolongum</i> ssp. <i>globosum</i>	BPS 01	DSMZ	DSM 26456	02.10.2012	Probiotal SpA
181	<i>Lactobacillus fermentum</i>	LF15	DSMZ	DSM 26955	01.03.2013	Probiotal SpA
182	<i>Lactobacillus fermentum</i>	LF16	DSMZ	DSM 26956	01.03.2013	Probiotal SpA
183	<i>Lactobacillus casei</i>	LC03	DSMZ	DSM 27537	24.07.2013	Probiotal SpA
184	<i>Lactobacillus crispatus</i>	LCR03	DSMZ	DSM 27538	24.07.2013	Probiotal SpA
185	<i>Lactobacillus jensenii</i>	LJE01	DSMZ	DSM 27539	24.07.2013	Probiotal SpA
186	<i>Lactobacillus helveticus</i> ID 922	LH01	DSMZ	DSM 28153	04.12.2013	Probiotal SpA
187	<i>Lactobacillus helveticus</i> ID 923	LH02	DSMZ	DSM 28154	04.12.2013	Probiotal SpA
188	<i>Lactococcus lactis</i> ssp. <i>cremoris</i> ID 1612	LLC02	DSMZ	DSM 28155	04.12.2013	Probiotal SpA
189	<i>Lactococcus lactis</i> ssp. <i>cremoris</i> ID 1252	LLC03	DSMZ	DSM 28156	04.12.2013	Probiotal SpA
190	<i>Lactococcus lactis</i> ssp. <i>Lactis</i> ID 1254	LLL01	DSMZ	DSM 28157	04.12.2013	Probiotal

191	<i>Bifidobacterium longum</i>	BL 01	DSMZ	DSM 28173	11.12.2013	Probiotal SpA
192	<i>Bifidobacterium longum</i>	BL 02	DSMZ	DSM 28174	11.12.2013	Probiotal SpA
193	<i>Bifidobacterium animalis</i> ssp. <i>lactis</i>	Bb1	DSMZ	DSM 17850	23.12.2005	BioMan Srl
194	<i>Streptococcus thermophilus</i>	ST 16 BM	DSMZ	DSM 19526	13.07.2007	BioMan Srl
195	<i>Bifidobacterium infantis</i>	BI 04	DSMZ	DSM 28651	08.04.2014	Probiotal SpA
196	<i>Bifidobacterium infantis</i>	BI 05	DSMZ	DSM 28652	08.04.2014	Probiotal SpA
197	<i>Streptococcus thermophilus</i>	ST 15	DSMZ	DSM 28911	11.06.2014	Probiotal SpA
198	<i>Streptococcus thermophilus</i>	ST 16	DSMZ	DSM 28912	11.06.2014	Probiotal SpA
199	<i>Streptococcus thermophilus</i>	ST 17	DSMZ	DSM 28913	11.06.2014	Probiotal SpA
200	<i>Lactobacillus fermentum</i>	LF 18	DSMZ	DSM 29197	30.07.2014	Probiotal SpA
201	<i>Lactobacillus fermentum</i>	LF 19	DSMZ	DSM 29198	30.07.2014	Probiotal SpA
202	<i>Leuconostoc</i> sp.	LM01	DSMZ	DSM 29372	10.09.2014	MoIn Srl

203	<i>Leuconostoc</i> sp.	LM10	DSMZ	DSM 29373	10.09.2014	Mofin Srl
204	<i>Leuconostoc</i> sp.	LM11	DSMZ	DSM 29374	10.09.2014	Mofin Srl
205	<i>Leuconostoc</i> sp.	LM12	DSMZ	DSM 29375	10.09.2014	Mofin Srl
206	<i>Lactobacillus plantarum</i>	LP10	DSMZ	DSM 29389	10.09.2014	Mofin Srl
207	<i>Lactobacillus plantarum</i>	LP11	DSMZ	DSM 29390	10.09.2014	Mofin Srl
208	<i>Lactobacillus plantarum</i>	LP12	DSMZ	DSM 29400	10.09.2014	Mofin Srl
209	<i>Lactobacillus plantarum</i>	LP13	DSMZ	DSM 29401	10.09.2014	Mofin Srl
210	<i>Lactobacillus pentosus</i>	LPS03	DSMZ	DSM 29402	10.09.2014	Mofin Srl
211	<i>Lactobacillus reuteri</i>	LRE10	DSMZ	DSM 29403	10.09.2014	Mofin Srl
212	<i>Lactobacillus brevis</i>	LBR02	DSMZ	DSM 29404	10.09.2014	Mofin Srl
213	<i>Lactobacillus salivarius</i>	LS 07	DSMZ	DSM 29476	09.10.2014	Probiological SpA
214	<i>Bifidobacterium breve</i>	BR 05	DSMZ	DSM 29494	09.10.2014	Probiological SpA
215	<i>Lactococcus lactis</i> ssp. <i>cremoris</i>	LCC02	DSMZ	DSM 29536	22.10.2014	Probiological SpA
216	<i>Bifidobacterium longum</i>	BL 21	DSMZ	DSM 29884	15.01.2015	Probiological SpA
217	<i>Lactobacillus rhamnosus</i>	LR 09	DSMZ	DSM 29885	15.01.2015	Probiological SpA
218	<i>Lactobacillus kefir</i>	LKE01	DSMZ	DSM 32027	08.04.2015	Probiological SpA

219	<i>Lactobacillus kefir</i>	LKE02	DSMZ	DSM 32056	29.05.2015	Probiotal SpA
220	<i>Lactobacillus acidophilus</i>	LA10	DSMZ	DSM 32075	03.07.2015	Probiotal SpA
221	<i>Lactobacillus kefirifaciens</i>	LKR01	DSMZ	DSM 32076	03.07.2015	Probiotal SpA
222	<i>Lactobacillus kefir</i>	LKF01	DSMZ	DSM 32079	10.07.2015	Probiotal SpA
223	<i>Lactobacillus kefir</i>	LKF02	DSMZ	DSM 32080	10.07.2015	Probiotal SpA
224	<i>Streptococcus thermophilus</i>	ST18	DSMZ	DSM 32134	03.09.2015	Mofin S.r.l.
225	<i>Streptococcus thermophilus</i>	ST19	DSMZ	DSM 32135	03.09.2015	Mofin S.r.l.
226	<i>Streptococcus thermophilus</i>	ST20	DSMZ	DSM 32136	03.09.2015	Mofin S.r.l.
227	<i>Streptococcus thermophilus</i>	ST21	DSMZ	DSM 32137	03.09.2015	Mofin S.r.l.
228	<i>Streptococcus thermophilus</i>	ST22	DSMZ	DSM 32138	03.09.2015	Mofin S.r.l.
229	<i>Streptococcus thermophilus</i>	ST23	DSMZ	DSM 32139	03.09.2015	Mofin S.r.l.
230	<i>Streptococcus thermophilus</i>	ST24	DSMZ	DSM 32140	03.09.2015	Mofin S.r.l.
231	<i>Lactobacillus salivarius</i>	LS02	DSMZ	DSM 32204	13.11.2015	Probiotal

232	<i>Weissella confusa</i>	WC01	DSMZ	DSM 32156	22.09.2015	Mofin S.r.l.
233	<i>Weissella confusa</i>	WC02	DSMZ	DSM 32157	22.09.2015	Mofin S.r.l.
234	<i>Lactobacillus curvatus</i>	LCU01	DSMZ	DSM 32160	22.09.2015	Mofin S.r.l.
235	<i>Lactobacillus plantarum</i>	LMC1	DSMZ	DSM 32252	29.01.2016	Probiotal SpA
236	<i>Lactobacillus reuteri</i>	LMC3	DSMZ	DSM 32253	29.01.2016	Probiotal SpA
237	<i>Lactobacillus parasei</i>	LMC4	DSMZ	DSM 32254	29.01.2016	Probiotal SpA
238	<i>Lactobacillus reuteri</i>	LMC5	DSMZ	DSM 32255	29.01.2016	Probiotal SpA
239	<i>Lactobacillus rhamnosus</i>	LMC6	DSMZ	DSM 32256	29.01.2016	Probiotal SpA
240	<i>Lactobacillus rhamnosus</i>	LMC7	DSMZ	DSM 32257	29.01.2016	Probiotal SpA
241	<i>Lactobacillus paracasei</i>	LMC8	DSMZ	DSM 32258	29.01.2016	Probiotal SpA
242	<i>Lactobacillus reuteri</i>	LMC9	DSMZ	DSM 32259	29.01.2016	Probiotal SpA
243	<i>Lactobacillus rhamnosus</i>	LMC10	DSMZ	DSM 32260	29.01.2016	Probiotal SpA

244	<i>Lactobacillus fermentum</i>	LF25	DSMZ	DSM 32275	15.03.2016	Probiotical SpA
245	<i>Lactobacillus fermentum</i>	LF5	DSMZ	DSM 32277	18.03.2016	Probiotical SpA
246	<i>Lactobacillus fermentum</i>	LF20	DSMZ	DSM 32288	14.04.2016	Probiotical SpA

Materials and Methods

Experimental protocol

The experiment was conducted on a group of 6 volunteers, all female and aged between 29 and 41 years (mean age 34.5 years).

Each volunteer tested 5 formulations of melatonin (gel 0.1%, gel 0.2%, gel 1%, cream, Circadin 2mg), with a wash-out period of one week after each application.

The saliva samples were taken according to the following experimental scheme:

h 10.00 Basal

h 10.30 30'

h 11.00 1h

h 13.00 3h

h 16.00 6h

The saliva was collected with Salivette (Sarstedt), following the instructions attached thereto (mouth rinsing before each sampling, chewing on the swab for 1 minute). The saliva was extracted from the swab by 2 min centrifugation at 4000 rpm, then divided into 300 µl aliquots and frozen at -20°C until the time of analysis.

Data analysis

The melatonin assays were performed with the ELISA (Enzyme-Linked Immunosorbent Assay) technique, using the Melatonin (direct) Saliva kit (SLV-4779 – DRG Instruments, Germany). The analytical sensitivity and inter- and intra-assay coefficients of variation are the following: 0.3 pg/ml, 7.6 – 13.0 % and 6.1 – 10.8 %.

The kit in question is certified for in-vitro diagnostic use.

Patient ID	Gel 0.1% 1 mg/g					
1	0.42	6.65	7.91	18.2	14.6	37.76
2	0.33	4.88	4.22	4.72	2.33	16.48
3	0.1	1.6	1.62	7.55	2.09	10.94
4	1.93	17.9	22.4	18.7	9.46	70.39
5	0.1	5.67	9.59	2.43	1.67	19.46
6	0.14	14.4	8.35	10.10	8.70	71.56
	Basal	30'	1h	3h	6 h	total
					Total 47.87	226.04 mean=37.67

CLAIMS

1. A composition in the form of a gel for topical use comprising:

- an effective amount of an active substance selected from the group comprising or, alternatively, consisting of:

(i) at least one microorganism selected from the group comprising or, alternatively, consisting of: live lactic bacteria, live bifidobacteria, biologically active bacteria or active bacterial components, extracts or cell components, bacterial enzymes, tyndallized bacteria, lysed bacteria, sonicated bacteria and peptidoglycans; and

(ii) melatonin and/or the natural and/or synthetic derivatives thereof; and

- a vehicle or carrier comprising water, a thickening viscous matrix comprising or, alternatively, consisting of at least one poloxamer or a mixture of poloxamers and, optionally, additives and/or excipients and/or adjuvants selected from among those capable of promoting the formation and stabilisation of the gel, selected from the group comprising or, alternatively, consisting of acid salts, sodium sorbate, potassium sorbate, sodium benzoate, potassium benzoate, glycols, ethylene glycol and propylene glycol;

wherein said composition comprises or, alternatively, consists of an effective amount of a microorganism

(i) selected from the group comprising or, alternatively, consisting of the microorganisms in Table 1; preferably said at least one microorganism is selected from the group comprising or, alternatively, consisting of the strains: *Lactobacillus salivarius* (LS01) DSM 22775, deposited on 23.07.2009; *Bifidobacterium breve* (BR03) DSM 16604, deposited on 20.07.2004; *Lactobacillus pentosus* (LPS01) DSM 21980, deposited on 14.11.2008; *Streptococcus thermophilus* (FP4) DSM 18616, deposited on 13.09.2006; *Lactobacillus casei* ssp. *rhamnosus* (LR04) DSM 16605, deposited on 20.07.2004; and *Lactobacillus acidophilus* (LA02) DSM 21717, deposited on 06.08.2008; even more preferably the strain is *Lactobacillus salivarius* (LS01) DSM 22775, and/or *Bifidobacterium breve* (BR03) DSM 16604, and/or *L. pentosus* (LPS01) DSM 21980, and

wherein said composition is for topical transdermal use in the preventive and/or curative treatment of pathologies, disorders or diseases associated with/deriving from alterations of the immune system selected from the group comprising allergies, atopy, allergic rhinitis, food hypersensitivity, dermatitis, atopic dermatitis, eczema, psoriasis, asthma and immunodeficiencies.

2. The composition for use according to claim 1, wherein said poloxamer is selected from the group comprising or, alternatively, consisting of Poloxamer 124 CAS N. 9003-11-6 with an average molecular weight of 2090-2360, Poloxamer 188 (Lutrol® F66) CAS No. 9003-11-6 with an average molecular weight of 7680-9510, Poloxamer 237 with an average molecular weight of 6840-8830, Poloxamer 338 with an average molecular weight of 12700-17400, Poloxamer 407 (Lutrol® F127 Prill) CAS No. 9003-11-6 with an average molecular weight of 9840-14600, or mixtures thereof; preferably said Poloxamer 188 is present in

an amount comprised from 0.1% to 10% by weight, out of 100 g of composition, preferably in an amount comprised from 0.5% to 5% by weight, for example from 1% to 3% by weight; and/or preferably said Poloxamer 407 is present in an amount comprised from 1% to 40% by weight, out of 100 g of composition, preferably in an amount comprised from 5% to 30% by weight, for example from 10% to 20% by weight.

3. The composition for use in accordance with one of claims 1-2, further comprising, as an active substance (iii), an effective amount of at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs.

4. The composition for use in accordance with any one of the preceding claims, wherein:

- said microorganisms are present at a concentration comprised from 1×10^6 CFU/g to 1×10^{12} CFU/g of composition, preferably from 1×10^7 CFU/g to 1×10^{11} CFU/g of composition, even more preferably from 1×10^8 CFU/g to 1×10^{10} CFU/g of composition, for example 1×10^9 CFU/g of composition, and wherein:
- said microorganisms are present in said composition in an amount by weight comprised from 0.1% to 5%, preferably in an amount by weight comprised from 0.5% to 3%, even more preferably in an amount by weight comprised from 1% to 2%, relative to the total weight of composition.

5. The composition for use in accordance with claim 1 or 2, wherein:

- said composition comprises an effective amount of an active substance selected from:
 - (iii) at least one compound selected from the group comprising or, alternatively, consisting of a flavonoid such as rutin, rutoxides, arbutin, oxerutin, diosmin, hesperidin and troxerutin, chemotherapeutic agents, arctigenin, arctin, berberine, berbamine, sanguinarine and chelerythrine, as such or in the form of plant extracts containing said compounds, on their own or in combination with one or more chemotherapeutic agents or anti-tumour drugs; and/or
 - (ii) melatonin and/or the natural and/or synthetic derivatives thereof;
- said active substance being present in said composition in an amount by weight comprised from 0.1% to 10% by weight, preferably in an amount comprised from 0.5% to 5% by weight, even more preferably from 1% to 3% by weight, relative to the total weight of the composition.

6. The composition in accordance with any one of claims 1-5, for use:

- in the treatment of pathologies, disorders or diseases due to the pathological malfunctioning of physiological functions connected with circadian rhythms;
- in the treatment of pathologies, disorders or diseases due to an abnormal or excessively high or excessively low blood pressure;
- in the treatment of pathologies, disorders or diseases due to an excess of free radicals and oxidative stress;
- in the treatment of pathologies, disorders or diseases due to an imbalance of the immune system;
- in the treatment of pathologies, disorders or diseases due to inflammatory states;
- in the treatment of pathologies, disorders or diseases due to acquired immunodeficiency;
- in the treatment of pathologies, disorders or diseases due to viral infections and bacterial infections;
- in a treatment as a support or adjuvant to chemotherapy;
- in the treatment of cancer with chemotherapeutic agents;
- in the treatment of sleep disorders in order to favour, in the treated subjects, the quality of sleep and regularity of sleep, with particular reference to REM sleep;
- in the treatment of pathologies, disorders or diseases of the eyes, of the retina, of the iris, of the optic nerve, retinal detachment and macular degeneration;
- in the treatment of vision disorders, in particular in maculopathy of the retina, via external applications in the vicinity of the eye and the temple;
- in the treatment of pathologies, disorders or diseases due to autism and Down's syndrome, in particular in children and adolescents, by favouring balance and control also of states of anxiety;
- in the treatment of pathologies, disorders or diseases due to senile dementia or Alzheimer's disease;
- in the treatment of pathologies, disorders or diseases due to Parkinson's disease or neurological dysfunctions, by improving sleep and tremors;
- in the treatment of pathologies, disorders or diseases due to pulmonary cystic fibrosis in children, by performing an anti-inflammatory activity;
- in the treatment of prostate tumours, by preventing the propagation thereof;
- in the treatment of tumours, as an anti-inflammatory, anti-tumour adjuvant;
- in the treatment of pathologies, disorders or diseases due to heart attack, myocardial infarction, cardiopathies, cardiac or coronary failure or myocardial insufficiency.

7. A process for the preparation of a composition in accordance with any one of the preceding claims, said process comprising the following steps:

- mixing in water, under continuous stirring, the various components, added in succession one after the other or separately premixed and added together, using a mixer provided with a temperature control and adjustment means and a stirring means, wherein the temperature is set at values lower than room

temperature, comprised from 2°C to 16°C, preferably from 4°C to 10°C, for example from 6°C to 8°C, for a time comprised from 1 minute to 15 minutes so as to obtain a homogeneous mixture;

- maintaining said homogeneous mixture, preferably under continuous stirring, at a temperature comprised from 2°C to 10°C, preferably at a temperature comprised from 4°C to 8°C, for example from 5°C to 7°C, for a time comprised from 1 minute to 60 minutes, preferably from 5 minutes to 40 minutes, even more preferably from 10 minutes to 20 minutes, so as to obtain said composition in a liquid state;

- packaging said composition in sealed containers.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053206

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/06 A61K47/10 A61K35/745 A61K35/747 A61K31/365
A61K31/4045 A61K31/4375 A61K31/4741 A61K31/4748 A61K31/7048
A61P9/10 A61P9/12 A61P11/00 A61P11/06 A61P17/00

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 practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/243384 A1 (ESCAMES ROSA GERMAINE [ES] ET AL) 28 August 2014 (2014-08-28)	1-6
Y	page 1, paragraph 1 page 6, paragraph 79 -----	7
X	WO 02/074325 A1 (GLENN GREGORY M [US] ET AL) 26 September 2002 (2002-09-26) page 49, line 8 - page 51, line 11 -----	1,2,6
Y	AROONSRI PRIPREM ET AL: "Effect of Polymeric Combinations on Mucoadhesive and Swelling Properties of Orabase Gel Formulations", ADVANCED MATERIALS RESEARCH, vol. 853, 24 December 2013 (2013-12-24), pages 3-8, XP055338521, DOI: 10.4028/www.scientific.net/AMR.853.3 the whole document ----- -/--	7



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

5 September 2017

Date of mailing of the international search report

12/09/2017

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053206

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 101 54 324 A1 (MERZ PHARMA GMBH & CO KGAA [DE]) 7 August 2003 (2003-08-07) page 3, paragraph 15 page 7, paragraph 55 page 9 - page 10; examples 1,5,7 -----	1-7
A	WO 2010/062153 A1 (GARCIA PEREZ MIGUEL ANGEL [MX]) 3 June 2010 (2010-06-03) page 1, paragraph 2 page 20, paragraph 1 - page 22, last paragraph -----	1-7
A	EP 1 769 821 A1 (INFECTIO RECHERCHE INC [CA]) 4 April 2007 (2007-04-04) page 7, paragraph 22-26 -----	1-7
A	WO 00/71139 A2 (REID GREGOR [CA]; BRUCE ANDREW W [CA]) 30 November 2000 (2000-11-30) the whole document -----	1-7
A	WO 2006/013441 A2 (PROGE FARM SRL [IT]) 9 February 2006 (2006-02-09) the whole document -----	1-7
A	WO 2008/058755 A1 (ABBOTT GMBH & CO KG [DE]; PETERSEN ROLF [DE]) 22 May 2008 (2008-05-22) page 7, paragraph 2 page 9, paragraph 2 page 18, paragraph 2 page 20 - page 21; examples 1,2 page 32 - page 34; example 15 -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/053206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014243384 A1	28-08-2014	AU 2012324752 A1 BR 112014009456 A2 CA 2851754 A1 CN 103945843 A EP 2702992 A1 ES 2384798 A1 JP 6038933 B2 JP 2014530844 A MX 342976 B RU 2014119858 A US 2014243384 A1 WO 2013057354 A1	01-05-2014 25-04-2017 25-04-2013 23-07-2014 05-03-2014 12-07-2012 07-12-2016 20-11-2014 19-10-2016 27-11-2015 28-08-2014 25-04-2013
WO 02074325 A1	26-09-2002	CA 2445486 A1 CN 1516595 A EP 1381381 A1 JP 2004525921 A WO 02074325 A1	26-09-2002 28-07-2004 21-01-2004 26-08-2004 26-09-2002
DE 10154324 A1	07-08-2003	AT 297221 T DE 10154324 A1 EP 1308169 A1 ES 2240634 T3 PT 1308169 E	15-06-2005 07-08-2003 07-05-2003 16-10-2005 31-10-2005
WO 2010062153 A1	03-06-2010	NONE	
EP 1769821 A1	04-04-2007	AR 018194 A1 AT 355050 T AU 762461 B2 BR 9909801 A CN 1302215 A CN 1597008 A DE 69935325 T2 EP 1079802 A2 EP 1769821 A1 ES 2284250 T3 HK 1037861 A1 HU 0101507 A2 ID 26791 A JP 4665075 B2 JP 2002512180 A NO 20005310 A NZ 507609 A PL 344111 A1 RU 2224503 C2 SK 15822000 A3 TR 200003074 T2 TR 200102067 T2 US 6500460 B1 US 2003133969 A1 WO 9953897 A2	31-10-2001 15-03-2006 26-06-2003 22-01-2002 04-07-2001 23-03-2005 15-11-2007 07-03-2001 04-04-2007 01-11-2007 14-12-2007 28-03-2002 08-02-2001 06-04-2011 23-04-2002 21-12-2000 26-09-2003 08-10-2001 27-02-2004 06-08-2001 22-01-2001 21-06-2002 31-12-2002 17-07-2003 28-10-1999
WO 0071139 A2	30-11-2000	AU 4905400 A CA 2374938 A1 WO 0071139 A2	12-12-2000 30-11-2000 30-11-2000
WO 2006013441 A2	09-02-2006	AT 419859 T	15-01-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/053206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 1778258 A2	02-05-2007
		ES 2320685 T3	27-05-2009
		PT 1778258 E	31-03-2009
		WO 2006013441 A2	09-02-2006

WO 2008058755 A1	22-05-2008	CA 2669392 A1	22-05-2008
		EP 2099420 A1	16-09-2009
		US 2010047297 A1	25-02-2010
		WO 2008058755 A1	22-05-2008
