The present invention regards a composition comprising trehalose, an antioxidant and at least one pharmaceutical excipient and the use of said composition for the treatment and the prevention of skin diseases and eye disorders.
Declarations under Rule 4.17:
— of inventorship (Rule 4.17(iv))
The present invention regards a composition comprising trehalose, an antioxidant and at least one pharmaceutical excipient and the use of said composition for the treatment and the prevention of skin and eye diseases.

The exposure of the skin to UV radiations may have serious consequences which, according to the duration of the exposure and predisposition of the subject, may include a simple erythema, photoageing and occurrence of melanoma or a skin cancer of different type from melanoma (non-melanoma skin cancer, NMSC). From an epidemiological point of view, non-melanoma skin cancers, such as basal cell carcinoma and squamous cell carcinoma (Bowen's disease), are about 80% of skin cancers.

The exposure of the skin to ultraviolet rays (UV) may lead to photo-induced DNA damage, in particular UVB rays (290-320 nm) have a direct mutagen action on the DNA and UVA rays (320-400 nm) have an indirect mutagen action through the formation of free radicals (see WO2014006645 and references mentioned therein).

The beginning and progression of non-melanoma skin cancers lead to a complex series of molecular alterations. Generally, in patients affected by NMSC there are observed photo-induced lesions at different stages of progression, which reflect the skin cell damage by the UV radiations, in particular UV-A and UV-B radiations.

It is generally deemed that the mechanism of formation of the photo-induced damage at
skin level comprises the interaction between UV radiations and DNA of epidermal cells. In particular, the DNA sites with adjacent pyrimidine bases are the preferred sites of formation of the photo lesions induced by UV rays, with formation of pyrimidine dimers, such as CPDs (cyclobutane pyrimidine dimers).

CPDs may be repaired by enzymes naturally present in the cell nucleus which operate by excision of the damaged nucleotides. Examples of enzymes which cooperate in this type of repair are helicases, endonucleases, DNA polymerases and ligases. In most organisms, CPDs may be repaired by the photolyase enzymes, which act after photoactivation.

CPDs may be generated by UV-B or UV-A radiations. It is known that the protection of human skin against damage to DNA caused by UV-A radiations is very low (Mouret, S. et al. Proc Natl Acad Sci USA 2006, 103, 13765).

The formulations currently known for the prevention of the photo-induced skin damage and diseases derived therefrom are agents which block the radiations (high SPF solar filters) and which should be applied before any exposure to radiations. Compositions containing enzymes and other substances capable of repairing damage to DNA (see for example WO2013098743), are also known. However, these compositions only act on damage initially caused to nucleic acids and they do not block damages that may be caused by radiations on the protein in vivo, for example by breaking sulphide bridges and for inducing protein aggregation. Damages at protein level are the first to be directly caused by radiation, while damage to DNA is always delayed.

In addition, due to the presence of said formulations it is necessary to isolate and purify enzymes capable of repairing DNA, which involves a tedious procedure and high costs. Furthermore, enzyme-based repairs may require particular preservation conditions (for
example at low temperature) so as to avoid or delay the degradation of active ingredients.

Lastly, preparations containing DNA repair enzymes - in the light of the high specificity of the catalytic mechanisms that characterise them - have an action limited on some photo-products on DNA (such as CPDs), but without specifically acting on the wholeness of the proteome.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a composition for the prevention and treatment of damages caused by UV radiations, and diseases associated thereto, without the disadvantages of the prior art compositions.

Another object of the present invention is to provide a topical composition capable of contrasting the ageing of the skin.

According to the present invention, these and other objects which shall be more apparent hereinafter, are attained through a topical composition comprising trehalose in combination with suitable excipients or diluents, as claimed in the claim.

DESCRIPTION OF THE DRAWINGS.

Figure 1 shows the Western blot analysis carried out on nuchal bioptic samples taken from 10 patients of beclin protein and amyloid peptides respectively measured at baseline and after 45 days of treatment with a topical composition of the invention containing trehalose encapsulated in liposomes.

Figure 2 shows, in quantitative form, the results of the Western Blot analysis referred to by figure 1 carried out on nuchal bioptic samples taken from 10 patients of beclin protein and amyloid peptides respectively measured at baseline and after 45 days of treatment with a topical composition of the invention containing trehalose encapsulated
in liposomes.

DETAILED DESCRIPTION OF THE INVENTION

These objects were attained through a composition as described above for use in the treatment or prevention of a disorder and/or of a skin disease, skin and eye annexes caused by exposure to solar radiations, ultraviolet or ionising in a subject, and for use in the treatment and prevention of skin ageing.

In the present invention, the expression powder trehalose is used to indicate trehalose that is not contained in liposomes.

In the present invention, the expression trehalose in liposomal or liposome form is used to indicate trehalose contained or comprised in liposomes.

In the present invention, the two "and/or" conjunctions - which join two components - are used to indicate that the component after this expression is present in association with the component before the aforementioned expression. Thus, the conjunction is "and"; or the component can be present as an alternative to the first component of said expression, in this case the "or" conjunction is applied.

In the present invention, the term excipient is used to indicate a substance commonly used in the formulation of pharmaceutical or cosmetic preparations or medical devices, as known to a man skilled in the art.

In the present invention, the expression divalent manganese is used to indicate the Mn$^{2+}$ ion which can be present in free, hydrated or complexed form, for example as a chelate, in form of salt, conjugate, oxide, suspension or aqueous solution. In particular, in the invention manganese ascorbate, manganese aspartate, manganese bisglycinate or manganese pidolate may be used.

The expression dermatoheliosis or photoageing is used to indicate the chronic and
progressive damage of the skin caused by the harmful action of ultraviolet rays on the skin cells. Dermatoheliosis or photoageing occurs through a series of lesions of various levels including wrinkles, loss of skin elasticity, occurrence of skin dyschromia and fine telangiectasias, deterioration and compaction of elastic fibres in the superficial dermal layer, ephelides, actinic keratosis, purpura, vascular lesions such as angiomas and telangiectasias, sebaceous hyperplasia and skin tumours.

The term "proteome" is used to indicate the entirety of the proteins of an organism or biological system, i.e. proteins produced by the genome. In particular, in the present invention, the term "proteome" indicates the entirety of the proteins of skin cells that can be damaged due to exposure to solar, ultraviolet (UVA and UV-B as defined above) or ionising radiations.

Unless otherwise specified, in the present invention the percentages shall be deemed to refer to the weight of a component to the total weight of the composition.

In one aspect, the present invention regards a composition comprising trehalose, an antioxidant and at least one excipient suitable for pharmaceutical use.

It was observed that the use of an association of trehalose with an antioxidant allows limiting or repairing the damage caused by UV radiations to the proteome of the skin cells.

It was observed that the application of trehalose in association with an antioxidant performs an action of preventing photo-induced cell damage, in particular preventing and repairing alterations on the cell proteome by the UV radiations.

In this case, it was observed that the application of a mixture of trehalose and an antioxidant, through topical skin administration, is very efficient when trehalose is contained in a liposome.
In the composition according to the present invention trehalose is comprised in a liposome when the topical application regards the skin and it is in particular applied in this form for the treatment and prevention of skin ageing.

Liposomes are vesicles formed by lipids, generally phospholipids or cholesterol, that may have dimensions varying between 2.5 nm and 1 µm by diameter. They are normally constituted by at least one double spherical and closed layer of phospholipids or cholesterol.

It was observed that the use of trehalose in a liposome allows obtaining a high concentration of active ingredient at epidermis and dermis level, which guarantees an efficient action of preventing photo-induced damage on proteome, as well as fighting skin ageing.

Liposomes can be prepared by utilising microfluidification techniques (as described in EP2633852, US5853753 and references mentioned therein), i.e. for self-aggregation of phospholipids in an aqueous phase in which the amphiphilic molecules of the phospholipids spontaneously generate spherical vesicles (double layers) to try to segregate the hydrophobic part of their molecules from the aqueous environment, while the polar part remains at contact with the aqueous phase.

The method for preparing liposomes comprises 3 steps: hydration of phospholipids, dimensioning of liposomes and removal of non-encapsulated material. Hydration occurs through a mechanical method: a thin lipid film is deposited by a solution in organic solvent on the wall of a glass flask (rotating evaporator). The film is hydrated under stirring at a temperature higher than the critical temperature of the phospholipid having the highest critical temperature. This allows obtaining multilamellar vesicles (MLV) with large dimensional distribution (greater than 0.1 µm). As regards the dimensioning
and dimensional distribution of the liposomes, the homogenisation method is used: the dimensional distribution curve is narrowed making the dispersion of liposomes pass through a high pressure homogeniser. This allows obtaining a bimodal dimensional distribution (with two maximum frequencies), with particles around 1,000 nm.

The last step consists in removing the organic solvent and all non-encapsulated material. The INCI (International Nomenclature of Cosmetic Ingredients) formula of the liposomes containing Trehalose at 5% by weight/total weight of the liposome (PMLs containing Trehalose) according to the present invention is: water, butylene glycol, trehalose, hydrogenated lecithin, carbomer, carrageenan (Chondrus crispus), sodium phosphate, sodium hydroxide, sodium hydroxymethylglycinate.

By way of non-limiting example, liposomes in the composition of the present invention may comprise (all percentages are by weight/ total weight of the liposome): 0.25-2.75% of butylene glycol, 0.04-0.44% of phospholipids, 0.0005 - 0.0055% of carrageenan, 0.0028 - 0.0308% of carbomer, 0.75-0.85% of sodium phosphate, 0.10-0.12% of sodium hydroxymethylglycinate.

The PMLs in the composition of the present invention may have, for example, a dimension between 500 and 1000 nm and/or a pH comprised between 5.5 and 7.0 preferably between 5.7 and 6.7.

Trehalose in liposomal form (PMLs containing Trehalose as described above) may be used for the formulation of creams, gels, lotions, sprays and solutions with the following excipients: with regards to creams, water, oils, emulsifiers, preservatives, pH corrector; with regards to gels, water, rheological additives, preservatives, pH corrector; with regards to lotions and spray, water, dispersants, preservatives, pH corrector. Generally, the formulations may be applied 1 to 3 times a day according to dosages
regarding the sites to be treated.

Trehalose in liposomal form may be used in concentration between 0.01 and 10% by weight/weight of the liposome and it is associated, in various concentrations, to powder trehalose, ectoine, carnosine, ergothioneine and manganese.

Preferably, the composition according to the invention comprises liposomes having a dimension between 500 and 1000 nm. Preferably, liposomes in the composition according to the invention comprise trehalose amounting to 1-10% by weight/weight of the liposome, more preferably 1-5% by weight/weight of the liposome.

Preferably, in liposomes in the composition according to the invention, the phospholipids are hydrogenated soy lecithin.

Preferably, in the composition according to the invention the liposomes comprising trehalose range between 90 and 99% by weight/total weight of the composition. (I deleted the entire sentence since the range of trehalose in liposomal form is the same, independent of the type of antioxidant present)

In the composition according to the invention the antioxidant is selected from among powder trehalose at least one amino acid such as ergothioneine, a peptide such as carnosine, ectoine (1,4,5,6-tetrahydro-2-methyl-4-pyrimidine-carboxylic acid), a salt or a divalent manganese complex and their mixtures. More preferably, the antioxidant is at least one from among powder trehalose, ergothioneine, ectoine, carnosine, a salt or a divalent manganese complex and their mixtures. More preferably the antioxidant is a salt or a divalent manganese complex. More preferably the antioxidant is selected from among powder trehalose and ectoine.

More preferably, the composition according to the invention comprises - as a salt or a divalent manganese complex - at least one among manganese ascorbate, manganese
aspartate, manganese bisglycinate or manganese pidolate.

Preferably, the amount of divalent manganese in the composition of the invention is between 0.01 and 0.1% by weight/total weight of the composition.

Preferably, the amount of ectoine in the composition of the invention is between 0.001 and 2% by weight/total weight of the composition, more preferably between 0.1 and 0.2.

Preferably, the amount of ergothioneine in the composition of the invention is between 0.005 and 1% by weight/total weight of the composition.

Preferably, the amount of carnosine in the composition of the invention is between 0.1 and 5% by weight/total weight of the composition.

Preferably, the composition of the invention comprises powder trehalose, more preferably at an amount between 1 and 10% by weight/total weight of the composition.

It was observed that in presence of powder trehalose, in addition to trehalose in liposomal form, there is obtained the advantageous synergic effect which results in effects for the prevention and treatment of damages caused to proteome by UV radiations exceeding the effects of the sum of the single components of the composition.

The composition of the present invention may be in a form known to a man skilled in the art and suitable for administering to a subject, human or animal, through topical means, for example as cosmetic composition, pharmaceutical composition or medical device.

The term "medical device" comprises a preparation with prevalent physical and/or mechanical effect. Examples of medical device in the present invention are creams, gels and lotions.

Preferably, the composition of the present invention is in a form suitable for
administering to a subject, human or animal, through topical means directly on the point
where exposure to radiations occurred or will occur.

More preferably, the composition of the present invention is in form of cream, gel, spray
or lotion suitable for topical use or as solution, suspension or spray for ophthalmic use.

In case of ophthalmic use, the composition of the present invention comprises trehalose
and/or trehalose in non-liposome form.

By way of non-limiting example, below are some non-limiting examples of ophthalmic
formulation according to the present invention and formulation for skin use, for use in
the treatment of diseases caused by exposure to solar, ionising and ultraviolet radiations.

FORMULATION 1 - ophthalmic solution

powder trehalose 3.821% p/v
manganese pidolate 0.015% p/v
sodium chloride q.s. for isotonicity
dibasic and monobasic potassium phosphate q.s. at pH 7
purified water q.s. at 100 ml

Formulation 2 ophthalmic solution

powder trehalose 3.821% w/V
ectoine 0.2% w/V
sodium chloride q.s. for isotonicity
dibasic and monobasic potassium phosphate q.s. at pH 7
purified water q.s. at 100 ml

Formulation 3 OPTHALMIC SPRAY

powder trehalose 1% w/w
ectoine 0.02% w/w
anhydrous sodium chloride 0.8% w/w
sodium hydroxymethylglycinate 0.2% w/w
disodium EDTA 0.1% w/w
trehalose in liposomal form 10% w/w
lactic acid 0.18% w/w
purified water q.s. at 100 ml
FORMULATION 3 FOR SKIN USE
dimethicone 18.5% w/w
zinc oxide 12% w/w
tocopherol 0.2% w/w
sodium dehydroacetate 1.6% w/w
disodium EDTA 0.1% w/w
trehalose in liposomal form 5% w/w
powder trehalose 1% w/w
nicotinamide 4% w/w
chlorophenesin 0.3% w/w
purified water q.s. at 100 ml

In another aspect, the present invention regards the composition comprising trehalose in liposomal form and an antioxidant as described above for use in the treatment or in the prevention of a skin/skin and eye annexes disorder and/or disease, caused by exposure to solar, ultraviolet or ionising radiations or by oxidative damage in a subject. Said disorder and/or disease is one from among melanoma, skin cancer different from melanoma, dermatoheliosis (photoageing) or oxidative damage in a subject. More preferably, said disorder and/or disease is dermatoheliosis (photoageing).
Preferably, the composition according to the present invention is applied from one to three times a day.

An embodiment of the present invention is described hereinafter by way of non-limiting example.

The protection effects of liposomes containing trehalose (final concentration: 5% by weight/weight of the culture) in combination with different antioxidants (each at a concentration of 3%) on UVB-induced damage were examined in vitro using HaCaT keratinocyte cultures. HaCaT, a cell line of non-oncogenic immortalised human keratinocytes, was maintained in DMEM to which there was added 10% of fetal bovine serum and 1% antibiotics in standard conditions of cell culture (37°C, 5% CO₂ in a humidified incubator). Radiation with UVB radiations was carried out using a Spectrolinker XL -1500 (Spectronics, Westbury NY, USA), UV polymerising device which emits most of its energy in the UVB range (280-320 nm) with a peak at 312 nm. The UV dose was measured with a UVX Radiometer (UVP Inc., Upland, CA, USA).

The cells were exposed to UVB radiation at a dose of 20 mJ/cm². Antioxidants and cytoprotective compounds (manganese, ectoine, carnosine, ergothioneine) were tested as regards their protective effect combined with liposomes containing trehalose.

The main markers used are apoptosis markers (fragmentation of DNA) and proinflammatory molecules levels (IL-1β and TNF-a).

For the detection of apoptosis, the DNA fragmentation percentage was evaluated 24 hours after treatment with the Sellins and Cohen method. In brief, about 3 x 10⁶ cells were lysed using 200 ml of lysis buffer and centrifuged at 13000 g for 10 min. Subsequently, DNA from all samples in the supernatant and pellets was precipitated in trichloroacetic acid 12.5% (TCA) at 4°C overnight and quantified using diphenylamine
reagent after hydrolysis in 5% TCA at 90°C for 20 min. The percentage of fragmented DNA for each sample was calculated as the amount of DNA in the supernatant divided by the total DNA for that sample (supernatant plus pellet). A Western blot analysis is carried out to detect the expression levels of IL-1β and TNF-α in irradiated HaCaT using specific antibodies. The results are expressed in arbitrary units (regarding the non-irradiated sample) and summarised in table 1.

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>UVB</th>
<th>B (TLL)</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragmented DNA</td>
<td>1 11.3 ± 2.5</td>
<td>5.4 ± 1.8</td>
<td>4.5 ± 1.4</td>
<td>3.2 ± 0.7</td>
<td>4.4 ± 1.0</td>
<td>4.3 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>1 24.7 ± 5.4</td>
<td>12.8 ± 2.8</td>
<td>9.8 ± 1.9</td>
<td>6.4 ± 1.2</td>
<td>7.5 ± 2.0</td>
<td>6.5 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>1 15.8 ± 4.2</td>
<td>9.1 ± 2.7</td>
<td>5.4 ± 1.7</td>
<td>4.1 ± 1.1</td>
<td>6.4 ± 1.4</td>
<td>4.9 ± 1.5</td>
<td></td>
</tr>
</tbody>
</table>

A = non-irradiated

B = liposomes containing trehalose (TLL) without oxidant

C = TLL and manganese (ascorbate)

D = TLL and ectoine

AND = TLL and carnosine

F = TLL and ergothioneine

The main results indicate that the combination of liposomes containing trehalose and ectoine lead to a more considerable inhibition of UV-induced apoptosis, as proved by the DNA fragmentation assay. In addition, it was observed that treatment with liposome containing trehalose and ectoine attained a more efficient reduction in the UVB-induced expression of proinflammatory molecules (IL-1β and TNF-α) in HaCaT keratinocytes.

A further aspect of the present invention regards compositions for topical skin use containing trehalose in liposomal form for use in the prevention and treatment of skin
ageing.

As a matter of fact, the Applicant found that trehalose in liposome form preferably in concentrations comprised between 2 and 8% more preferably at concentrations of 5% is capable of fighting skin ageing.

The applicant experimentally revealed both at molecular level and from a clinical point of view the efficiency of topical application of liposomes containing trehalose (in particular at 5% concentrations in a carrier).

For this purpose, there was carried out a study in which there were recruited 10 subjects (8 females, 2 males; average age: 44.4 ± 3.8 years) with presence of crow’s feet wrinkles in the periocular region. The subjects applied liposomes containing trehalose (5% concentration in a carrier) for 45 days, in the entire face-neck area. Before (basal) and after treatment (and after 45 days), all subjects carried out punch biopsies at nuchal level.

The following parameters were evaluated at molecular level: activation of the autophagy and presence of beta-amyloid peptides at skin level (both evaluated at molecular level through the analysis of nuchal biopsies using the Western blot technique).

As a matter of fact, autophagy is a highly conserved degradation process in which pathological or aged proteins are sequestrated in a double membrane vesicle (autophagosome) and transported to the lysosomes for degradation. This activity was directly evaluated determining, through Western blot analysis, the variation of expression in nuchal skin biopsies, taken from the aforementioned patients, of beclin, a known autophagy marker (an increase of such marker represents an increase of autophagy), as well as indirectly evaluating (still through Western blot analysis) the skin
expression variation of peptides derived from amyloid, which is deemed a known skin ageing marker. Thus, the reduction of this parameter represents a direct demonstration of an increase of autophagy.

The results of these analyses carried out at molecular level are respectively indicated in Figure 1 and 2 and they were obtained by comparison using the housekeeping beta-actin protein expression as control.

There was observed an about 4 times increase after 45 days of application of the liposomes containing trehalose, of beclin with respect to the basal values. On the other hand, the skin expression of peptides derived from amyloid was reduced by 80% with respect to the basal, indirectly confirming the activation of the autophagy removal of pathological peptides associated to skin senescence.

With regards to clinical analyses, instrumental analyses were carried out at the level of the face of the study recruits, with the aim of determining the following parameters:

1) skin pigmentation homogeneity points,

2) hydration of the corneal layer and

3) visibility index of the crow's feet wrinkles.

The parameters were evaluated by analysing the facial skin surface and by corneometry and the results are indicated in the following table.
The obtained results were indicated in the following table 2.

<table>
<thead>
<tr>
<th></th>
<th>linsnl</th>
<th>45 days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour uniformity</td>
<td>7.4 ± 1.5</td>
<td>9.1 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hydration of the corneal</td>
<td>48.3 ± 14.1</td>
<td>59.1 ± 19.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>layer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crow's feet wrinkles volume</td>
<td>5.5 ± 1.3</td>
<td>5.0 ± 1.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Crow's feet wrinkles visibility</td>
<td>14.3 ± 4.2</td>
<td>11.5 ± 5.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

TABLE 2 - Analysis of the facial skin surface and corneometry

The data indicated in the table uniformly revealed statistically considerable improvements with regards to the uniformity of the skin colour, the hydration of the corneal layer and the crow's feet wrinkles visibility index. In particular, the increase of the skin autophagy represents an innovative mechanism for removing excess pigment at skin level. On the other hand, a reduction of the crow's feet wrinkles volume was observed by a clinically appreciable degree, although it was not statistically significant.
CLAIMS

1. A topical composition comprising trehalose, in combination with at least one excipient for a use selected from among:
   I) use for the prevention and treatment of a skin/skin or eye annexes disorder or disease caused by exposure to solar, ionising and ultraviolet radiations;
   II) use for the prevention and treatment of skin ageing wherein:
      I-A) when said use is for the prevention and the treatment of a skin/skin annexes disorder or disease caused by exposure to solar, ionising or ultraviolet radiations, trehalose is comprised in liposomes and said composition comprises at least one antioxidant agent selected from among powder trehalose, ectoine, ergothioneine, carnosine or a salt or a divalent manganese complex, and mixtures of said antioxidants,
      I-B) when said use is for the treatment or prevention of eye disease or disorder caused by exposure to solar, ionising and ultraviolet radiations said topical composition comprises trehalose contained in liposomes and/or powder trehalose and said antioxidant agent is selected from among ectoine, ergothioneine, carnosine, mixtures of said oxidants
   II) when said use is for the prevention and treatment of skin ageing, said topical composition comprises trehalose contained in liposomes.

2. The composition for topical use according to claim 1 wherein said disorder and/or disease caused by exposure to solar, ionising and ultraviolet radiations is selected from among melanoma, skin cancer different from melanoma, lesions caused by dermatoheliosis.

3. The composition for use according to claim 1 or 2 for the treatment and prevention of
lesions caused by dermatoheliosis.

4. The composition for use according to any one of claims 1-3, wherein the antioxidant is ectoine.

5. The composition for use according to claim 1, wherein said salt or divalent manganese complex is manganese ascorbate, manganese aspartate, manganese bisglycinate or manganese pidolate.

6. The composition for use according to any one of claims 1-5, in form of cream, gel, spray or lotion suitable for topical use, when said use is:

IA) for the treatment or prevention of a skin/skin annexes disorder or disease caused by exposure to solar, ionising or ultraviolet radiations, or:

II) for the prevention and treatment of skin ageing.

7. The composition for use according to claim 1, in form of solution, suspension or spray for ophthalmic use, when said use is for the treatment or prevention of eye disease or disorder caused by exposure to solar, ionising and ultraviolet radiations.
Figure 1

Figure 2
<table>
<thead>
<tr>
<th>ITALIANO</th>
<th>ENGLISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basale</td>
<td>Basal</td>
</tr>
<tr>
<td>Liposomi 45 gg</td>
<td>Liposomes 45 days</td>
</tr>
<tr>
<td>Beclina</td>
<td>Beclin</td>
</tr>
<tr>
<td>Beta actina</td>
<td>Beta actin</td>
</tr>
<tr>
<td>Peptidi amiloidi</td>
<td>Amyloid peptides</td>
</tr>
</tbody>
</table>