Title: COMPOSITION FOR PREVENTIVE TREATMENT OF COLD SORES

Abstract: The invention relates to a composition for the preventive treatment of fever blisters, including recurring fever blisters, wherein a composition, which comprises a physical UV filter, a zinc salt with antiviral action and an additive suitable for topical application, is preventively applied topically to parts of the face which can be affected by fever blisters. Preferred compositions, in particular stable oil-in-water emulsions, also form part of the invention.
COMPOSITION FOR PREVENTIVE TREATMENT OF COLD SORES

The present invention relates to a composition for preventive, topical treatment of the symptoms associated with the productive phase of infections by the Herpes Simplex Virus (HSV), such as fever blisters, including cold sores.

The Herpes Simplex Virus is a virus which infects nerve cells in mammals. In humans two types of HSV occur, HSV-1 mainly infects the nerve endings in the face, particularly the area around nose and mouth, while type 2 mainly infects the nerve endings in the anogenital area. The molecular reason for this tissue preference is unknown; nor is this an absolute preference, both HSV-1 and HSV-2 can be found in the facial area and in the anogenital area. Of adults in the US and Europe, 80% is carrier of HSV-1 and 20% is carrier of HSV-2.

The productive phase of the infection of the HSV manifests itself on the skin with one or more of the following symptoms: blisters, itching, a burning sensation and scab formation. If they occur in the face, these symptoms are referred to in common usage as 'fever blisters' or a 'cold sore' (herpes labialis) if the symptoms occur on the lips. These symptoms can affect the appearance of the face. Due to this, and the itching, a general feeling of discomfort can result in the patient with fever blisters.

In the infection the virus DNA integrates in the host DNA, were it remains for life as "provirus". The productive phase of the virus can be induced by the influence of environmental factors and host factors. Environmental factors which can herald a productive phase of HSV are sunlight (UV wavelength) and infectious diseases. Host factors which play a part in the
suppression of the productive phase are the immune system and the oxidation/antioxidation status. The recurrence of a productive phase is here often accompanied by a recurrence of one or more of the above described symptoms and the sensation of discomfort associated therewith.

The infection by both types of HSV is identical: the productive phase manifests itself on the skin with a burning and painful sensation with forming of blisters for 2-4 days (on average 3 days), followed by scab formation and wound healing for 4-7 days.

An HSV infection is generally harmless in adults with a fair to good all-round state of health, but can be life-threatening in newborn babies; probably because babies have not yet been able to build up an immune reaction to HSV.

It will be sufficiently apparent from the foregoing that an effective prevention of the productive phase of HSV infections is important, since fever blisters (including cold sores) can hereby be prevented.

Prevention of the productive phase of HSV infections and treatment of the symptoms of the productive phase, i.e. cold sores, with topical agents is known from the prior art.

Kneist et al. (Arzneimittelforschung 1995; 45(5):624-6) thus describe clinical data of the effectiveness of zinc sulphate in the symptomatic treatment of Herpes labialis recidivans.

Brody et al. (Br J Dermatol 1981; 104(2):191-4) describe the effect of topical administering of zinc sulphate on recurrent Herpes Simplex infections.

Kumel et al. (J Gen Virol 1990; 71 (Pt 12):2989-97) describe the molecular mechanisms possibly forming the basis of the inhibition of HSV infections by zinc ions.

In their opinion this inhibiting action is linked to an
inhibiting effect of the zinc ions on the function of a glycoprotein that plays a part in the penetration of the virion in the host cell.

American patent US 6475526 describes the topical use of a composition comprising a combination of a zinc compound and an antioxidant in the symptomatic treatment of HSV infections.

In addition to the topical use of zinc ions, the effectiveness of using a chemical sun filter on the skin has been researched by Rooney et al. in relation to recurrent herpes labialis (Lancet 1991 7;338(8780):1419-22). The authors conclude from their research that use of a (chemical) sun filter can be effective in the prevention of sunlight-induced recurrent infections.

The prior art thus describes on the one hand two distinct types of topical agents, zinc sulphate or a chemical sun filter, and on the other hand three distinct methods of employing these agents: (a) preventing cold sores by applying a chemical sun filter before the skin is exposed to sunlight; (b) applying zinc sulphate after the first signs of a cold sore have manifested themselves and continuing to apply zinc sulphate until the cold sore has disappeared; and (c) the same as method 'b' but with the difference that, after the cold sore has disappeared, zinc sulphate is applied for life, periodically and according to a fixed regime, in order to prevent the cold sore from returning.

The agents and methods for their use mentioned in the prior art are insufficiently effective to prevent cold sores. It has thus been found that in many cases the application of only a UV-filter produces an insufficiently protective effect, probably because sunlight is only one of the factors which can induce a productive phase of HSV. It has further been found that
in many cases application of zinc sulphate alone produces an insufficiently protective effect in the case of exposure to sunlight, probably because zinc sulphate (in the concentration used) cannot prevent the productive phase of the Herpes virus from being induced at a determined quantity of sunlight, or because other factors which can initiate the productive phase can occur simultaneously with sunlight. Nor are the methods effective, since lifelong application of a medication is generally considered undesirable. This is moreover impractical and expensive. Against this background, applicant has been seeking more effective agents for preventing the productive phase of HSV infections and the fever blisters (including cold sores) associated therewith.

Applicant has found that the topical administering in the face of a combination of zinc ions and a physical UV filter, at the moment when the person in question is (possibly) at an increased risk of developing a fever blister, or certainly does not wish to develop a fever blister, is more effective in preventing fever blisters than that which is described in the prior art.

The invention therefore relates to a composition for the preventive treatment of fever blisters, in particular recurring fever blisters, wherein a composition, which comprises a physical UV filter, a zinc salt with antiviral action and an additive suitable for topical application, is preventively applied topically to parts of the face which can be affected by fever blisters.

The compositions according to the invention are effective in the prevention of fever blister due to their preventive effect on the development of the productive phase of an HSV infection, including a recurring HSV infection. Due to the link between fever
blisters and the productive phase of an HSV infection, fever blisters must be understood in the context of the present invention to also mean the productive phase of an HSV infection. Fever blisters are also understood to include a cold sore.

The composition according to the invention can be applied from the moment that there is (possibly) an increased risk of developing fever blisters, up until several days after the (possibly) increased risks have disappeared or are at least considerably reduced. An increased risk can result from exposure of the face to sunlight (UV radiation) but also from, among others, fatigue and/or stress and/or illness. Reference is intentionally made here to a '(possibly) increased risk', since fatigue and stress cannot usually be determined objectively. If a person who regularly has fever blisters wishes to be certain that he/she does not have fever blisters at a specific moment, he/she can also begin applying the composition according to the invention several days before this specific moment.

The composition is generally applied to the face, such as on the parts around the mouth and nose, for instance on the lips, in the case of an anticipated increased exposure to UV radiation or in the case of stress or fatigue. Application of the composition can be stopped several days after the increased risk has disappeared. In addition, the composition as described above can be applied to the described parts of the face several days prior to the moment at which fever blisters are absolutely undesired. The moment at which the fever blisters are undesired may be a period of a number of days. The composition according to the invention is then applied to the parts of the face which can be affected by fever blisters for several days before this period of time and up to the last day of this period of time. In
the context of the present invention, several days are here 1-5 days, for instance 1, 2, 3 or 4 days.

During the period of its use the composition according to the invention can be applied as often as necessary to the parts of the face which can be infected by HSV. The composition is preferably applied to the parts of the face where fever blisters have already occurred before. It is generally sufficient to apply the composition 1-3 times a day, and the composition is preferably applied 2 or 3 times a day. In the case of an increased exposure to UV radiation, it is however recommended to apply the composition to the skin at intervals of 2-4 hours during this increased exposure.

In the context of the present invention, an increased exposure to UV radiation is understood to mean a prolonged period of exposure as well as an increased radiation intensity. The UV radiation can originate from a natural source, such as the sun, or from an artificial source.

The compositions according to the invention comprise a physical UV filter. The advantage of using a physical UV filter over a chemical filter is the long-lasting action, since in contrast to a chemical filter a physical filter is not converted by the radiation. In addition, there occur no, or at least fewer, hypersensitivity reactions to the physical UV filters.

Hypersensitivity reactions can bring about inflammation reactions which, when they occur in the face, can also be accompanied by an effect on the appearance of the face.

The physical UV filter comprises zinc oxide or titanium dioxide or a combination hereof as active constituent. The quantity and form of the physical UV filter is such that a composition is obtained with a sun protection factor (SPF) greater than 12, preferably
greater than 15, most preferably greater than 20. In addition, it is recommended that the physical UV filter does not essentially contribute toward the colour of the composition according to the invention. The quantity and form of the physical UV filter is preferably such that, despite its presence, an essentially transparent composition can be manufactured. The physical filter is preferably a finely or ultra-finely distributed material, such as a micronized material, for instance micronized zinc oxide or micronized titanium dioxide, since this reduces the colour effect. The average size of the particles is herein smaller than about 5 μm, for instance smaller than about 2 μm, preferably smaller than about 1 μm, more preferably smaller than about 0.05 μm, such as 0.02 μm. Suitable quantities of the physical UV filter (zinc oxide and/or titanium dioxide) lie between 4-20% (w/w), preferably 8-12% (w/w), such as 10% (w/w) relative to the total weight of the composition. As physical UV filter a combination of zinc oxide and titanium dioxide is preferably applied in a ratio of 5:1 to 2:1, preferably 3:1 to 2:1, most preferably 3:1. In order to obtain a good UV-screening action, it is important to suspend the particles of the physical UV filter uniformly in the composition.

In addition to the physical UV filter, the composition according to the present invention also comprises as active constituent a zinc salt with antiviral action. The zinc salt with antiviral action is preferably a water-soluble zinc salt, since the ions hereof can be disassociated to a great extent, whereby the zinc ions can be released. Zinc salts which can be used within the scope of the present invention can be chosen from the group comprising zinc sulphate, zinc chloride, zinc acetate, zinc citrate, zinc nitrate, zinc tartrate, zinc maleate, zinc lactate, zinc amino
acetate, zinc aspartate, zinc glutamate, zinc propionate, zinc gluconate, zinc butyrate, zinc formiate, zinc glyceride, zinc glycolate, or their hydrates. Zinc sulphate is recommended.

In respect of the zinc ions, the quantity of the zinc salt with antiviral action in the composition according to the invention can be between 0.005-2.0% (w/w), preferably 0.1-1% (w/w), more preferably 0.5-1% (w/w) relative to the total weight of the composition. A water-soluble zinc salt will be present substantially only in a water phase or a water-miscible phase. In respect of the zinc ions the quantity of the zinc salt can therefore also be expressed relative to the quantity of water (water-miscible phase) and amounts in that case to 0.07-5% (w/w), preferably 0.17-2% (w/w) and more preferably 0.275-1.8% (w/w).

In addition to the active constituents, the composition according to the present invention comprises at least one additive suitable for topical use. The additive is preferably a carrier and/or diluent such as a fat or an oil, or a combination hereof.

Fats can be selected from one or more of lanette cream, cetomacrogol cream, wool fat, wool wax alcohols, preferably one or more of (white) vaseline and liquid paraffin. The proportion of fat in the composition according to the invention can lie between 5-30% (w/w), such as 10-20% (w/w), preferably 15-20% (w/w).

Oils can be selected from one or more of arachide oil, oleic acid, canola oil, corn oil, cotton-seed oil, ethyl oleate, isopropyl palmitate, sesame oil, soya oil and cetiol V. The proportion of oil in the composition can lie between 10 and 30% (w/w), such as 15-20% (w/w).

The composition according to the invention will further contain water or another polar solvent, such as propylene glycol, for the purpose of dissolving the
water-soluble zinc salt with antiviral action and making free zinc ions available. The use of water as polar solvent is recommended, since it is readily available and is cosmetically well tolerated. The water or other polar solvent is preferably added in a quantity of 40-70% (w/w), such as 50-60% (w/w), preferably 55% (w/w).

If water is added in addition to an oil and/or fat carrier, an emulsion, more preferably a stable emulsion, is preferably formed from the water phase and oil/fat phase. Such an emulsion is preferably an oil (fat) in water (O/W) emulsion, wherein the water phase is the continuous (outer) phase and the oil (fat) phase is the discontinuous (enclosed) phase. Because in an O/W emulsion the water phase is included as outer phase, the water-soluble zinc salt is readily available for absorption by the skin when the composition according to the invention is applied thereto. In a water in oil (fat) (W/O) emulsion, the water phase is enclosed in the oil phase, whereby the water-soluble zinc salt is less readily available for absorption by the skin.

In order to emulsify the water and oil phase, one or more emulsifiers can be added to the composition according to the invention. A stable emulsion is preferably formed using the emulsifier. A stable emulsion is here understood to mean an emulsion wherein, for an extended period of time such as longer than a week, preferably longer than a month, more preferably longer than 6 months, most preferably longer than a year, no separation of the oil (fat) phase and the water phase occurs and/or no transposition from an O/W emulsion to a W/O emulsion occurs.

It has been found that in particular a stable o/w emulsion is an exceptionally suitable presentation form of the composition according to the invention. As stated, in such an o/w emulsion the water-soluble zinc
salt is readily available for absorption by the skin. In addition, the physical UV-filter can be incorporated in the oil (fat) phase. This is particularly recommended if zinc oxide and/or titanium dioxide are applied as physical UV filter because of the hydrophobic properties of these substances. In a particularly preferred embodiment, the composition according to the invention in respect of the zinc ions, comprises, relative to the total composition, a quantity of zinc salt of 0.5-1% (w/w); 15-25%, preferably 20% of a fat, preferably a combination of white vaseline and liquid paraffin; 5-15%, preferably about 10% of a physical UV filter, preferably a 1:4, such as 1:3, combination of zinc oxide and titanium dioxide; 50-60%, preferably 52-58%, most preferably 55% (w/w) water; and an emulsifier which is suitable for forming an oil (fat) in water emulsion.

A suitable emulsifier can be selected from the group of cetyl and stearyl alcohol, Eumilgin B2 (cetomacrogol 1000), stearic acid, lanolin, lanolin alcohols, light and heavy mineral oils, petrolatum, beeswax, paraffin wax, tween derivatives, span derivatives or combinations thereof. The emulsifier can be applied in a quantity of 2-20% (w/w), such as 5-15% (w/w), preferably 7-12% (w/w). A combination of cetyl and stearyl alcohol and Eumilgin B2 (cetomacrogol 1000) is preferably used to emulsify the composition. This combination of cetyl and stearyl alcohol and Eumilgin B2 (cetomacrogol 1000) can be applied in a ratio of 1:5 to 5:1, preferably a ratio of 3:1. The combined quantity of cetyl and stearyl alcohol and Eumilgin B2 (cetomacrogol 1000) is for instance 7-12% (w/w), such as 10.5% (w/w).

One or more detergents, such as NaOH or laurenth sulphate, can further be added as additive. Addition of NaOH and/or laurenth sulphate can help bring about better penetration of the skin by the zinc ions.
Suitable applicable quantities of these additives are known to the skilled person.

As stated above, it is important for a good UV-protective action to distribute the particles of the physical UV filter uniformly through the composition. If the composition is an emulsion, such as an oil (fat) in water (O/W) emulsion, the particles can be suspended in the oil (fat) phase. If the oil (fat) phase is uniformly distributed in the water phase, the particles of the physical UV filter are hereby also distributed uniformly in the composition.

The composition according to the invention can take the form of a cream or gel. The advantage of a cream or gel is that it can be used in hygienic manner. When a cream or gel is used, the chance of cross-infection of different parts of the body, particularly the face, is hereby relatively low compared to for instance the use of a stick. If used hygienically, a cream or gel can even be used by a number of people, without the occurrence of, or at least with a reduced chance of, infection between the people mutually.

The composition according to the invention is preferably not visible after application to the skin, since it is transparent in colour or has a colour which corresponds with the colour of lips and/or is quickly absorbed by the skin. In addition, it is advantageous if the composition is water-resistant. This prevents it losing its effect under the influence of water. This is particularly important if the composition is applied to the parts around the mouth. The water-resistant properties prevent the composition disappearing quickly from the lips through contact with saliva and/or with the tongue. Use of, among others, vaseline and/or liquid paraffin as additive gives the composition water-resistant properties.
The composition according to the invention is preferably suitable for cosmetic use, and such cosmetic compositions with one or more of the above stated properties form a further aspect of the present invention.

The invention is further elucidated on the basis of the following exemplary embodiments. These exemplary embodiments must be deemed as practicable embodiments of the invention and in no way limit the scope of the invention.

Example I:

A transparent, water-resistant cream was obtained by mixing the components below in the stated ratio, and tubes with a content of 30 ml were filled with the cream.

- zinc oxide, average particle size 0.1 µm 10 g
- zinc sulphate 0.8 g
- liquid paraffin 44.6 g
- lanette cream 44.6 g

Example II:

A transparent, water-resistant cream was obtained by mixing the components below in the stated ratio, and tubes with a content of 50 ml were filled with the cream.

- zinc oxide, average particle size 0.05 µm 16 g
- zinc sulphate 2 g
- Vaseline 36.4 g
- lanette cream 145.6 g
Example III:

A transparent, water-resistant cream was obtained by firstly (i) mixing the following substances of component A in the stated quantities while heating to 75-80%:

A
Cetyl and stearyl alcohol 8.0 g
Emulgin B2 (cetomacrogol 1000) 2.5 g
Isopropyl myristate 1.5 g
White vaseline 10.0 g
Liquid paraffin 110-230 mpas 10.0 g
-------
Sub-total 32.0 g

Then (ii) the substances of component B were suspended in the still warm mixture of component A.

B
Pigment iron oxide red E 172 0.02 g
Zinc oxide 7.5 g
Titanium dioxide 2.5 g
-------
Sub-total 10.02 g

(iii) The following substances of component C were mixed with or dissolved in water of about 80°C.

C
Demineralized water (RO 80) 55.0 g
Zinc sulphate 1.0 g
Citric acid (for pH regulation) 0.4 g
Allantoin 1.5 g
Methyl parahydroxy benzoate 0.05 g
(as preservative)
Sub-total 57.98 g
total 100 g

(iv) The mixture of step (iii) was mixed with the mixture of step (ii) and the whole was cooled to about 30°C.

(v) Add 0.03 g of Menthae piperitae aetheroleum.

(vi) Tubes with a content of 50 ml were filled with the cream with an SPF of 20.
1. Composition for the preventive treatment of fever blisters, including recurring fever blisters, wherein a composition, which comprises a physical UV filter, a zinc salt with antiviral action and an additive suitable for topical application, is preventively applied topically to parts of the face which can be affected by fever blisters.

2. Composition as claimed in claim 1, wherein the composition is applied to the face from the moment that the user has an increased risk of developing fever blisters.

3. Composition as claimed in claim 2, wherein the composition is applied up until several days, such as 1-5 days, after the increased risk has disappeared.

4. Composition as claimed in claims 2-3, wherein the increased risk comprises an increased exposure to UV radiation, and the composition is applied at intervals of 2-4 hours during this increased exposure.

5. Composition as claimed in claim 1, wherein the composition is applied to the face for several days, such as 1-5 days, before the day(s) on which the user wishes to certainly not have fever blisters.

6. Composition as claimed in claim 5, wherein the composition is applied up to and including the day(s) on which the user wishes to certainly not have fever blisters.

7. Composition as claimed in any of the claims 1-6, wherein the zinc salt is water-soluble.

8. Composition as claimed in any of the claims 1-7, wherein the zinc salt is zinc sulphate.

9. Composition as claimed in any of the claims 1-8, wherein the composition in respect of the zinc ions
comprises a quantity of the zinc salt of 0.005-2.0\% (w/w), preferably 0.1-0.5\% (w/w).

10. Composition as claimed in any of the claims 1-9, wherein the UV radiation filter comprises zinc oxide and/or titanium dioxide.

11. Composition as claimed in claim 10, wherein the composition comprises between 4-20\% (w/w), preferably 8-12\% (w/w), such as 10\% (w/w) zinc oxide and/or titanium dioxide.

12. Composition as claimed in any of the claims 1-11, in the form of a cream or gel.

13. Composition as claimed in any of the claims 1-12, which further contains water in a quantity of 50-60\% (w/w), preferably 52-58\% (w/w), most preferably 55\% (w/w), and wherein the additive is an oil/fat-like substance and the water phase and oil/fat phase form an oil/fat-in-water emulsion.

14. Composition as claimed in claim 13, wherein the emulsion is a stable emulsion.

15. Composition as claimed in any of the claims 1-14, wherein the additive is selected such that the composition is water-resistant.

16. Composition as claimed in any of the claims 1-15, with a sun protection factor (SPF) of at least 12, preferably at least 15, and most preferably at least 20.

17. Cosmetic composition as claimed in any of the claims 1-16, comprising a physical UV filter, a zinc salt with antiviral action and an additive suitable for topical application.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)**

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO—Internal, WPI Data, PAJ, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>FR 2 824 474 A (PIERRE FABRE DERMOCOSMETIQUE S.A.) 15 November 2002 (2002-11-15) page 1, line 1 - line 4 examples 1,8 page 7, line 25 - line 30 claim 7</td>
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<td>Y</td>
<td>WO 99/47109 A (MERCK PATENT GMBH) 23 September 1999 (1999-09-23) page 3, line 24 - page 4, line 9 example claims</td>
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Further documents are listed in the continuation of box C. Patient family members are listed in annex.

| * Special categories of cited documents: |
| "A" document defining the general state of the art which is not considered to be of particular relevance |
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| "R" document: member of the same patent family |

Date of the actual completion of the international search: 25 May 2004

Name and mailing address of the ISA: European Patent Office, P.B. 5816 Patentlaan 2 NL—2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Epskamp, S

**Date of mailing of the international search report:** 09/06/2004
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