PCT WORLD INTELLECTUAL PROPER
International Bur

INTERNATIONAL APPLICATION PUBLISHED UNDER T

WO 9605805A1

(51) International Patent Classification 6 :
A61K 7/40, 31/09, 31/045

A1

(11) International Publication Number: **WO 96/05805**

(43) International Publication Date: 29 February 1996 (29.02.96)

(21) International Application Number: PCT/SE94/00782

(22) International Filing Date: 25 August 1994 (25.08.94)

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(81) Designated States: AT, AU, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KR, LV, NL, NO, NZ, PL, RO, RU, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOSITION FOR TREATMENT OF SKIN BLISTERS

(57) Abstract

A cream composition for treatment of or prophylaxis against skin blisters, such as blisters developing after sun-bathing, in solar dermatitis or in connexion with an infection by Herpes simplex virus comprises one member each straight chain primary aliphatic alcohols, preferably C_{12}-C_{22} straight chain alcohols, branched chain primary aliphatic alcohols, preferably C_{12}-C_{24} branched chain alcohols, and polyglycol ethers of primary aliphatic alcohols, preferably of C_{12}-C_{22} primary alcohols. The composition is free from pharmacologically active agents in amounts that are therapeutically effective in man. Methods of treatment, a process for manufacture of the composition and the use of the composition for the manufacture of a medicament are also disclosed.

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COMPOSITION FOR TREATMENT OF SKIN BLISTERS.

The present invention relates to a cream composition for treatment of or prophylaxis against skin blisters, such as blisters due to sun-bathing or solar dermatitis (polymorphic light-induced dermatitis) or blisters at or around the lips in connexion with infection by Herpes simplex virus.

Skin blisters are a widespread affection. They may arise from irritation of the skin by radiation, heat or mechanical or chemical agents, e.g., after taking a sun-bath. However, they are often caused by an infection such as a latent infection by Herpes simplex virus with recurrent outbursts in form of small blisters on or adjacent to the lips. These episodes do not require medical treatment but always cause distress. After a few days the blisters will heal, followed by a shorter or longer asymptomatic period. The blisters come with itch and are often touched by hand consciously or unconsciously, from which secondary infections may result.

The known antiviral agents acyklovir and phosphono formic acid have insignificant effect in topical treatment. Acyclovir shows effect in various kinds of herpes infections if given in tablet form or administered intravenously.

Cream compositions for treatment of Herpes simplex episodes based on these agents have been developed. Acyklovir eye ointment 3 % shows effect in Herpes simplex keratitis, that is, eye infection caused by Herpes simplex virus. A cream containing 5 % by weight of acyklovir does not show significant prophylactic effect against cold sores caused by Herpes simplex virus (Dermatologica 172 (1986) 104-107). The effect of the known cream is assumed to be due to the local action of the medicine on herpes virus inhibiting its reproduction and thereby alleviating the symptoms. To obtain the intended effect, it is important for the cream to be applied as soon as possible after the patient becomes aware of a coming active episode

and, preferably, also as an maintenance prophylactic measure. A drawback is the toxicity of the pharmacologically active compound. Because the cream is applied on the lips there is risk for unintended oral intake, especially in children.

The purpose with the present invention is to provide a cream for treatment of skin blisters of the kind mentioned above, which excludes the possibility of oral intake of toxic agents and which is effective even if administered when blisters already have developed.

According to the invention this purpose is met by a cream composition comprising at least one member from each of straight chain primary aliphatic alcohol, branched chain primary aliphatic alcohol and polyglycol ether of primary aliphatic alcohol, and which does not contain pharmacologically active agents, such as agents against Herpes simplex virus, in doses therapeutically effective in man. In this context, the term pharmacologically active agents does not relate to agents that have been cleared by registration authorities for formulation of creams, salves, lotions and similar pharmaceutical compositions, that is, pharmaceutical excipients, including preservatives for such compositions.

It is preferred for the straight chain aliphatic primary alcohol to be a C_{12}-C_{22} alcohol, for the branched chain aliphatic primary alcohol to be a C_{12}-C_{24} alcohol and for the polyglycol ether of straight chain aliphatic primary alcohol to be a polyglycol ether of a C_{12}-C_{22} alcohol.

It is particularly preferred for the composition according to the invention to comprise from 1.0 to 9.0 % by weight, more preferred from 3.5 - 7.0 % by weight, most preferred from 4.5 - 6.5 % by weight of C_{12}-C_{22} straight chain primary aliphatic alcohol.

It is also particularly preferred for the composition according to the invention to comprise from 0.5 to 5.5 % by weight, more preferred from 1.5 - 4.0 % by weight, most preferred from 2.5 - 3.5 by weight of C_{12}-C_{24} branched chain primary aliphatic alcohol.

Suitably the composition according to the invention comprises from 0.4 to 5.0 % by weight, more preferred from 1.0 - 3.5 % by weight, most preferred about 2 % by weight of polyglycol ether of C_{12}-C_{22} straight chain primary aliphatic alcohol.

According to a preferred aspect of the invention, the composition comprises consistency-controlling agent in an amount of between 3 and 15 % by weight, said consistency - controlling agent comprising one or several agents selected from the group consisting of mineral oil, silicone oil and paraffin wax. The composition according to the invention preferably comprises between 0 and 2.5 % by weight of mineral oil, between 0 and 2.0 % of silicone oil and between 0 and 12 % of paraffin wax.

Strongly hydrophobic agents, i.a., certain consistency-controlling agents such as fats of vegetable or animal origin, for example, lanolin or coconut oil, and, to a minor extent, hydrocarbons or hydrocarbon fractions, such as vaselinum album or vaselinum oil, when present in larger amounts reduce or entirely eliminate the effect of the cream according to the invention, whereby the overall content of these agents seems to be decisive. A more pronounced reduction in activity can be observed if saturated carbohydrate fractions with a molecular weight between about 150 to about 250, such as, e.g., vaselinum oil, are added to the composition according to the invention than on addition of corresponding fractions with higher molecular weight, such as, for example, paraffin wax. Reduced effect of a composition according to the

invention has been observed in the presence of fats in suntan creams and other cosmetic salves, oils, creams, lotions, etc. on the treated area.

These observations provide an indication about a possible mechanism for the blister-eliminating or blister-preventing effect of the composition according to the invention. It is possible that the cream affects the membrane function of the skin preventing the accumulation of liquid in the blisters or, rather, preventing the development of blisters by accumulation of liquid in the deeper layers of the skin or by effecting resorption of liquid that already has accumulated, that is, in the first case, by impeding the development of blisters and, in the second case, by making existent blisters shrink and vanish without formation of a crust. It is thus preferred for the composition according to the invention to be essentially free from fats of animal or vegetable origin.

As long as the basic composition of the cream is not substantially changed other agents may be added which are beneficial for the effect of the cream and have low or medium hydrophobicity.

It is thus preferred to add to the composition according to the invention, as required by the circumstances, pharmaceutical excipients, such as preservatives, preferably methyl paraban, propyl paraban or a mixture thereof, in a total amount between 0 and 0.8 % by weight, preferably between 0.05 and 0.3 % by weight, the composition further optionally containing one or several agents selected from the group consisting of colouring agents, perfumes, one or several pH-stabilizing agents, preferably selected from the group consisting of citric acid, tartaric acid, lactic acid and betaine lactate, emulsifiers, preferably sodium lauryl sulfate and sorbitan esters of higher fatty alcohols, agents for skin care,

preferably carbamide, local anaesthetics, UV-filtering agents and agents effective against other infections than by Herpes simplex, particularly antibiotics and steroids.

If so desired the symptom-treating effect according to the invention can be combined with an antiviral effect by the composition additionally containing antiviral agents that are effective against Herpes simplex virus in therapeutically effective dosages in man, particularly foscarnet or acyklovir or a mixture thereof. Also other antiviral agents may be used for this purpose, especially compounds of the nucleoside type.

It is obvious that the composition according to the invention has great value for the topical treatment of manifestations of infections by Herpes simplex virus in man and of skin blisters of other origin. It is also preferred to make up the composition according to the invention for this specific purpose, that is, to bring it into a form suited for practical use, therein included an appropriate package, such as a tube, a single dose package in plastic material or metal foil or a cream jar.

Surprisingly the manifestation of Herpes simplex labialis infection that generally is the most discomforting one to the patient, i.e., skin blisters, in that way can be kept at bay without taking recourse to pharmacologically active agents in the proper sense. In regard of toxicity the cream composition according to the invention is on par with some of the most lenient products for skin care on the market.

The invention also discloses a process for manufacture of a cream composition intended for prophylaxis against or treatment of skin blisters caused by radiation, heat or chemical or mechanical agents or caused by infections, particularly infection by Herpes simplex virus, comprising

emulsifying in water one or several agents selected from the group consisting of straight chain primary aliphatic alcohol, branched primary aliphatic alcohol and polyglycol ether of primary aliphatic alcohol, preferably by selection of at least one agent for each member of the group, in absence of pharmacologically active agents in concentrations that are therapeutically active in man, particularly agents with antiviral activity. It is preferred for the process according to the invention to comprise addition of consistency-providing agents. In addition, the process according to the invention may comprise addition of pharmaceutical excipients, such as preservatives, preferably methyl paraban, propyl paraban or a mixture thereof. The process according to the invention may also comprise the addition of colouring agents, perfumes, pH-stabilizing agents, emulsifiers, agents for skin care, UV-filtering agents, local anaesthetics, and agents against infections other than by Herpes simplex, particularly antibiotics and steroids. Also antiviral agents such as foscarnet or acyclovir may be added to the composition according to the invention.

Also disclosed is a method for topical treatment of blisters due to Herpes simplex labialis infection in man with a cream composition according to the invention as well as a method for the corresponding topical treatment of skin blisters in man due to physical or chemical irritation of the skin, such as blisters formed in solar dermatitis or sunburn blisters.

The composition according to the invention may be used for the manufacture of a medicament for topical treatment of blisters due to herpes simplex labialis infection in man or for the manufacture of a medicament for topical treatment of skin blisters in man due to physical or chemical irritation of the skin, such as blisters formed in solar dermatitis or sunburn blisters.

The invention will now be explained in greater detail by reference to several preferred but not limiting embodiments.

Example 1

55 g of cetyl alcohol, 30 g of 2-octyl dodecanol, 20 g of cetostearyl alcohol polyglycol ether, 5 g of mineral oil, 2.5 g of silicone oil and 55 g of paraffin wax were added to a 3 liter beaker. The mixture was heated on a water bath to 85° C under stirring. To 3 g of methyl paraben and 3 g of propyl paraben in a 2 l beaker 825 ml water was added and heated to 85° C under stirring. The aqueous solution was added to the mixture of the organic compounds and homogenized (1500 r.p.m.). Emulsification was stopped after 10 min, the mixture cooled to 30° C and homogenization continued for another 10 min. An opaque white cream was obtained which did not show any signs of phase separation after storing at room temperature for 8 weeks.

Example 2

By the same procedure as in Example 1 a cream was prepared from 80 g of cetyl alcohol, 30 g of 2-octyl dodecanol, 30 g of cetostearyl alcohol polyglycol ether, 20 g of vaselinum oil, 10 g of silicone oil, 55 g of paraffin wax, 3 g of methyl paraben, 3 g of propyl paraben and 755 ml of water. An opaque white cream was obtained.

Examples 3 - 8

By the procedure of Example 1 the following cream compositions were prepared:

Example	3	4	5	6	7	8
g/1000 g cream						
cetyl alcohol	90	70	55*)	55	35	15
2-octyl dodecanol	30	30	30	10	55	30
cetostearyl alcohol polyglycol ether	20	20	20	35	50	50
vaselinum oil	20	10	10	5	10	10
silicone oil	10	20	10	2.5	2.5	2.5
paraffin wax	55	55	30	30	55	55
methyl paraben + propyl paraben 1:1	3	3	3	3	3	3
rest water						

*) cetostearyl alcohol

Example 9 - 11

A cream with the composition according to Example 1 was prepared as described but with additional substances added, and with corresponding reduction in water content:

Example	added substance	g/1000 cream
9	lanolin	30
10	vaselinum album	30
11	coconut oil	30

Example 12

Skin test in persons having cold sores. Skin blisters in persons with mild Herpes simplex labialis infection were treated with cream compositions according to Examples 1 to 12. Treatment commenced when blisters started to appear. Cream was applied only to a limited part of the area covered by blisters or expected to be covered by blisters (1 - 3 persons tested per composition). Effect in form of

reduced average size of blisters/smaller number of blisters/quicker drying-up of blisters was observed with cream compositions according to Examples 1, 2, 6, 7 (good effect) and 3, 4, 5, 8 (fair effect). The compositions according to Examples 9 - 11 did not exhibit effect.

Example 13

Skin test in persons having solar dermatitis (polymorphic light-induced dermatitis). Nine women with solar dermatitis on the lower part of the neck manifest in form of itch and eczema were treated with cream of the composition according to Example 1. The itch stopped entirely after about one hour. The eczema disappeared in six of the test subjects after 3 to 4 hours.

Solar dermatitis heals within 1 - 2 days but the itch causes considerable distress. Solar dermatitis is normally treated topically with cortisone.

Example 14

Skin test on emerging sunburn blisters. Seven persons (5 women, 2 men) with beginning formation of blisters on their shoulders were treated twice the same day with a cream of the composition according to Example 1. On inspection next day the blisters were found to have disappeared. In absence of treatment, blisters remain for some days and result in scaling of the skin.

Claims

1. A Cream composition for treatment of or prophylaxis against skin blisters, such as blisters due to sun-bathing or in case of solar dermatitis (polymorphic light-induced dermatitis) or blisters at or adjacent to the lips in connexion with infection by Herpes simplex virus, characterized in that it comprises at least one member from each of straight chain primary aliphatic alcohol, branched chain primary aliphatic alcohol and polyglycol ether of primary aliphatic alcohol, and does not contain pharmacologically active agents, such as agents against Herpes simplex virus, in doses therapeutically effective in man.

2. The composition according to claim 1, characterized in that the straight chain primary aliphatic alcohol is a C_{12}-C_{22} alcohol, that the branched chain primary aliphatic alcohol is a C_{12}-C_{24} alcohol and that the polyglycol ether of primary aliphatic alcohol is a polyglycol ether of a C_{12}-C_{22} alcohol.

3. The composition according to claim 1 or 2, characterized in that it comprises from 1.0 to 9.0 % by weight, more preferred from 3.5 - 7.0 % by weight, most preferred from 4.5 - 6.5 % by weight of C_{12}-C_{22} straight chain primary aliphatic alcohol.

4. The composition according to any of claims 1 - 3 characterized in that it comprises from 0.5 to 5.5 % by weight, more preferred from 1.5 - 4.0 % by weight, most preferred from 2.5 - 3.5 % by weight of C_{12}-C_{24} branched chain primary aliphatic alcohol.

5. The composition according to any of claims 1- 4, characterized in that it comprises from 0.4 to 5.0 % by weight, more preferred from 1.0 - 3.5 % by

weight, most preferred about 2 % by weight of polyglycol ether of C_{12}-C_{22} primary aliphatic alcohol.

6. The composition according to claims 1 to 6, c h a r a c t e r i z e d in that it comprises consistency-controlling agent in an amount of between 3 and 15 % by weight, said consistency-controlling agent comprising one or several agents selected from the group consisting of mineral oil, silicone oil and paraffin wax.

7. The composition according to claim 6, c h a r a c t e r i z e d in that it comprises between 0 and 2,5 % by weight of mineral oil, between 0 and 2.0 % of silicone oil and between 0 and 12 % of paraffin wax.

8. The composition according to any of preceding claims, c h a r a c t e r i z e d in that it is essentially free from fats of animal or vegetable origin.

9. A method for topical treatment of blisters due to Herpes simplex labialis infection in man, wherein a pharmacologically effective amount of a cream composition according to any of claims 1 to 8 is applied to said blisters.

10. A method of topical treatment of skin blisters in man due to physical or chemical irritation of the skin, such as blisters formed in solar dermatitis or sunburn blisters, wherein a pharmacologically effective amount of a cream composition according to any of claims 1 to 8 is applied to said blisters.

11. The use of a composition according to any of claims 1 to 8 for the manufacture of a medicament for topical treatment of blisters due to infection by Herpes simplex virus in man.

12. The use of a composition according to any of claims 1 to 8 for the manufacture of a medicament for topical treatment of skin blisters in man due to physical or chemical irritation of the skin, such as blisters formed in solar dermatitis or sunburn blisters.

13. A process for manufacture of a cream composition for prophylaxis against or treatment of skin blisters caused by radiation, heat or chemical or physical agents or caused by infection, particularly infection with Herpes simplex virus, c h a r a c t e r i z e d in that it comprises emulsification in water of one member from each of straight chain primary aliphatic alcohol, branched chain primary aliphatic alcohol and polyglycol ethers of primary aliphatic alcohol, in the absence of pharmacologically active agents in amounts therapeutically effective in man, particularly agents with antiviral effect.

14. The process according to claim 13, c h a r a c t e r i z e d in that it comprises addition of consistency-controlling agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00782

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 7/40, A61K 31/09, A61K 31/045
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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	SE, A, 9300663-3 (CARL KAMME), 26 August 1994 (26.08.94), see the examples	1-8,11-14
A	EP, A2, 0055029 (KOWA CO LTD.), 30 June 1982 (30.06.82)	1-8,11-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
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"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
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Date of the actual completion of the international search	Date of mailing of the international search report
30 March 1995	13 -04- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00782

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/95

International application No.
PCT/SE 94/00782

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
SE-A- 9300663-3	26/08/94	NONE		
EP-A2- 0055029	30/06/82	SE-T3-	0055029	
		CA-A-	1179600	18/12/84
		JP-C-	1559987	31/05/90
		JP-A-	57098209	18/06/82