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Fortsættes ...



## DESCRIPTION

**[0001]** The present invention relates to compositions containing chitosan, a chitosan derivatives which is hydroxyalkyl chitosan or a physiologically acceptable salt thereof, and a short-medium chain dicarboxylic acid amide, or a physiologically acceptable salt thereof, for the preparation of a medicament, or a medical device, or a sanitary product, or a cosmetic, forming a film after application onto the skin of the face and of other affected areas, useful for protecting skin in rosacea, a chronic inflammatory condition of the skin, and other skin conditions characterized by teleangiectasia, like couperose and leg teleangiectasia.

### BACKGROUND OF THE INVENTION

**[0002]** Rosacea is a common but often misunderstood condition that is estimated to affect over 13 million people worldwide (Plewig & Jansen in: Fitzpatrick's Dermatology in General Medicine. Freedberg et al. Eds., 6th ed., McGRAW-HILL pub., NY 2003, p. 688). It affects white-skinned people of Celtic or northern European descent, and has been named the 'curse of the Celts'. It is rarer in dark-skinned people, like American and African blacks.

**[0003]** It begins as erythema (flushing and redness, also called "couperose") on the central face and across the cheeks, nose, or forehead but can also less commonly affect the neck and chest. As rosacea progresses, other symptoms can develop such as semi-permanent erythema, teleangiectasia (dilation of superficial blood vessels on the face), red domed papules (small bumps) and pustules, red gritty eyes, burning and stinging sensations, and in some advanced cases, a red lobulated nose (rhinophyma). The disorder can be confused with, and co-exist with acne vulgaris and/or seborrheic dermatitis. Rosacea affects both sexes, but is almost three times more common in women, is common in the third and fourth decade and peaks between the ages of 40 and 50 years. The presence of rash on the scalp or ears suggests a different or co-existing diagnosis, as rosacea is primarily a facial diagnosis.

**[0004]** The pathogenesis of rosacea is unknown, and various factors have been suspected to contribute to this condition. Among the various factors, the following have been claimed to play a role: degenerative changes of the perivascular/ vascular collagen, that lead to small vessel dilatation resulting in flushing, teleangiectasia, erythema; perivascular leakage of potentially inflammatory substances; abnormal tissue response to cytokines and other mediators; use of topical drugs (corticosteroids). Exposure to temperature extremes can cause the face to become flushed as well as strenuous exercise, heat from sunlight, severe sunburn, cold wind, moving from cold to hot environment. There are also some foods and drinks that can trigger flushing, these include alcohol, caffeine (hot tea and coffee), and spicy food. Microorganism also have been claimed to contribute to the development or complicate rosacea, like *Demodex folliculorum*, *Helicobacter pylori* or *Propionibacterium acnes*.

**[0005]** Treatment of rosacea is inconclusive. Systemic or topical treatments include antibiotics, metronidazole and antifungals; retinoids, some beta blockers, spironolactone. No causal treatment has ever been proposed, and lifelong symptomatic treatment is often necessary, as just few cases may go into a permanent remission of the symptoms. Long term treatment of rosacea is limited by the intrinsic toxicity of drugs.

**[0006]** Leg teleangiectasia consists in very thin varicose capillaries, with calibre within 0,1 and 1 mm, that are classified as follows:

1. 1) Teleangiectasia due to venous insufficiency, accompanied by other clinical signs of venous insufficiency. They are localized at the foot back, retromalleolar region, legs, and at the medial thigh surface.
2. 2) Teleangiectasia due to hormonal abnormalities, localized at the medial and anterolateral thigh surface. They spontaneously occur during menarche, menopause, pregnancy or under contraceptive treatment.
3. 3) Very thin teleangiectasia due to constitutional weakness of the capillary system, mainly at the distal portion of the legs. This is triggered by UV radiation, and by hot and cold temperature.
4. 4) Matting type teleangiectasia
5. 5) Reticular varicose veins: in most cases they represent the nourishing veins for the districts that are interested by telengectasia.

**[0007]** No satisfactory treatment exists for leg teleangiectasia and the only possible treatment is aesthetic surgery.

**[0008]** Thus, there is an unsatisfied need of safe and active medical tools to protect a skin that is unusually vulnerable to

chemical and physical insults.

**[0009]** Chitosan and its derivatives are amino-polysaccharides, derived from the chitin extracted from the exoskeleton of the crustaceans, known in the art for their use in different preparations. KR20020084672 discloses chitosan as an ingredient of microspheres, useful as a carrier for separation of proteins or peptides; KR20020048534 reports chitosan as an ingredient of a pack composition for skin massage, including paraffin wax as an effective component; JP2005306746 is teaching the use of chitosan to obtain a wrinkle therapeutic agent as an ingredient of gel-like or spongy preparations of botulinus toxin. WO2005055924 reports chitosan derivatives as ingredients of hydrogels useful for cavity-filling wound dressings. JP2004231604 teaches compositions of chitosans having a high deacetylation degree, as an ingredient of a carrier sheet with a porous spongy texture. WO03042251 discloses compositions comprising chitosan in the form of a network of nano-sized fibres. WO02057983 discloses a multilayered, air gap sheet of chitosan with a regular lamellar structure which retains drugs for a prolonged period of time; JP11060605 teaches an amphiphilic chitosan derivative which can be used as dispersion stabilizer or emulsifier in a drug for application to skin. Finally, EP1303249, discloses a nail varnish composition containing at least one antimycotic agent and an hydroxyalkyl or a carboxyalkyl chitosan, whereas WO2004/112814 discloses a nail restructuring composition based on one herb extract from the genus Equisetum in combination with hydroxypropyl chitosan.

# **DESCRIPTION OF THE INVENTION**

**[0010]** It has now surprisingly been found that preparations containing chitosan or its derivatives, which are hydroxyalkyl chitosans, and at least the amide of a short-medium chain (from 6 to 12 carbon atoms) aliphatic dicarboxylic acid may form an elastic film onto the skin, after application and drying, suitable to protect the skin from chemical or physical insults. The two components of the film, saccharidic and lipidic, act in a synergistic way and have a protective activity superior to that of the two components alone.

**[0011]** The film forming compositions according to the present invention may easily be sprayed onto the skin surface, by allowing quick drying and easy formation of an elastic film, that avoids bothersome sensation of oily skin. The film forming compositions according to the present invention may also be applied on the skin by gently massage. The film formed after drying protects the skin from the insult of both hot and cold temperature, decreases the inflammation due to ultraviolet radiation and prevents the growth of microorganisms by coating them and inhibiting their vital functions.

**[0012]** The object of the present invention is thus represented by a pharmaceutical and/or cosmetic composition containing:

1. (A) at least chitosan, a chitosan derivative which is hydroxyalkyl alkyl chitosan and/or a physiologically acceptable salt thereof, and;
2. (B) at least a C<sub>6</sub>-C<sub>12</sub>-dicarboxylic acid amide and/or a physiologically acceptable salt thereof.

**[0013]** Said composition is useful to form a film after application onto the skin and drying, that protects the skin of the face and the other areas affected by rosacea as well as by other skin conditions characterized by telangiectasia.

**[0014]** Chitosan derivatives are hydroxyalkyl chitosans, such as hydroxypropyl chitosan, being the claimed water soluble chitosans derivatives.

**[0015]** Among the C<sub>6</sub>-C<sub>12</sub>-dicarboxylic acids, C<sub>8</sub>-C<sub>16</sub>-dicarboxylic acids are particularly preferred, C<sub>9</sub>-dicarboxylic acids being the most preferred; according to additional preferred embodiments, such dicarboxylic acids are linear and/or alkyl acids.

**[0016]** The C<sub>6</sub>-C<sub>12</sub>-dicarboxylic acid amide which is used for the purposes of the present invention is preferably represented by the following formula:



wherein:

"n" is comprised between 4 and 10, preferably between 6 and 8 and, more preferably, it is 7;

R is a -N(R')(R'') group, wherein:

R' is H or a C<sub>1</sub>-C<sub>4</sub>-alkyl group, and

R" is H, a C<sub>1</sub>-C<sub>4</sub>-alkyl group or a C<sub>1</sub>-C<sub>4</sub>-carboxy group.

[0017] According to preferred embodiments, said C<sub>1</sub>-C<sub>4</sub>-alkyl groups are methyl or ethyl whereas said C<sub>1</sub>-C<sub>4</sub>-carboxy group is carboxy methyl.

[0018] The preferred C<sub>6</sub>-C<sub>12</sub>-dicarboxylic acid is azelaic acid. Among C<sub>6</sub>-C<sub>12</sub>-dicarboxylic acid amides, azelaic acid amides, such as azeloyl diglycine, are thus preferred, and may be in form of a salt, preferably a sodium or potassium salt, such as potassium azeloyl diglycinate.

[0019] The composition according to the present invention may be applied by a gently massage on the skin, or may be sprayed by allowing the formation of an elastic film after drying. The composition according to the present invention allows a long lasting intimate contact and continuous protection of the skin for many hours after the application.

[0020] Compositions according to the present invention are in the form are in the form of liquid, semiliquid or semisolid preparations, including solutions, suspensions, lotions, emulsions, colloids, creams, gels, with a content in component A from 0.1 to 10 wt.% (percentages by weight are given with respect to the whole preparation), preferably from 0.2 to 5 wt.%, more preferably from 0.25 to 2.0 wt.% and with a content in component B from 0.1 to 30 wt.% (percentages by weight are given with respect to the whole preparation), preferably from 0.25 to 25 wt.%, more preferably from 0.5 to 20 wt.%.

[0021] Compositions according to the present invention are superior to the conventional formulations, in that they leave an uniform and invisible film. Moreover, compositions according to the present invention do not dirty, do not dry like gels and lotions do, and do not give bothersome sensation when applied, like other rigid film preparations do.

[0022] Pharmaceutical compositions are prepared according to conventional technique, using compatible excipients, adjuvants and/or pharmaceutically or cosmetically acceptable carriers, and may contain, in combination, other active principles with complementary or, in any case, useful activity.

[0023] Examples of these compositions prepared according to the present invention include: solutions, emulsions, suspensions, colloids, creams, gels, for application to affected skin.

[0024] The compositions according to the present invention may contain one or more additional ingredients selected from solvents, sunscreens, skin-conditioning agents, emollients, moisturizers, emulsifying agents, viscosity-increasing agents, UV-A filters, plant extracts, antioxidants.

[0025] The pharmaceutical compositions and the uses of the present invention will now be more fully described by the following examples. It should, however, be noted that such examples are given by way of illustration.

#### **Example 1**

[0026] An oil in water cream having the following w/w % composition was prepared:

1.	POTASSIUM PALMITOYL HYDROLYZED WHEAT PROTEIN	1.00%
2.	GLYCERYL STEARATE	2.00%
3.	CETEARYL ALCOHOL	2.00%
4.	GLYCERYL STEARATE SE	1.00%
5.	DICAPRYLYL ETHER	4.00%
6.	ETHYLHEXYL METHOXYCINNAMATE	4.00%
7.	BUTYL METHOXYDIBENZOYLMETHANE	1.00%
8.	LECITHIN	0.02%
9.	TOCOPHEROL	0.001%

10.	ASCORBYL PALMITATE	0.001%
11.	CITRIC ACID	0.001%
12.	TOCOPHERYL ACETATE	0.50%
13.	PURIFIED WATER	81.00%
14.	HYDROXYPROPYL CHITOSAN	0.50%
15.	XANTHAN GUM	0.50%
16.	DENATURATED ETHYL ALCOHOL	1.00%
17.	PHENETHYL ALCOHOL	0.50%
18.	CAPRYLYL GLYCOL	0.50%
19.	POTASSIUM AZELOYL DIGLYCINATE	0.50%

**Preparation****[0027]**

Phase A: Hydroxypropyl chitosan was dispersed in ca. 50%wt of total water until a clear solution was obtained. The solution was heated at  $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and Xanthan gum was added and stirred until a homogenous solution was obtained.

Phase B: Potassium palmitoyl, Glyceryl Stearate, Cetearyl Alcohol, Glyceryl Stearate SE, Dicaprylyl Ether, Ethylhexyl methoxycinnamate, Butyl methoxydibenzoylmethane, Lecithin, Tocopherol, Ascorbyl Palmitate, Citric Acid and Tocopheryl Acetate were mixed together and heated at  $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$ .

**[0028]** Phase B was added to Phase A under agitation (turbo) to allow the emulsification. The resulting emulsion was cooled to  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  under continuous mixing.

**[0029]** Caprylyl Glycol dissolved into Phenethyl Alcohol, Potassium Azeloyl Diglycinate dissolved in the rest of purified water (50%wt) and Ethyl Alcohol were mixed into the emulsion at the end of preparation. The product was kept under gentle agitation until a homogenous oil in water cream was obtained.

**Example 2**

**[0030]** An oil in water cream having the following w/w % composition was prepared:

1.	POTASSIUM PALMITOYL HYDROLYZED WHEAT PROTEIN	3.00%
2.	GLYCERYL STEARATE	5.00%
3.	CETEARYL ALCOHOL	5.00%
4.	GLYCERYL STEARATE SE	3.00%
5.	DICAPRYLYL ETHER	6.00%
6.	ETHYLHEXYL METHOXYCINNAMATE	6.00%
7.	BUTYL METHOXYDIBENZOYLMETHANE	3.00%
8.	LECITHIN	0.04%
9.	TOCOPHEROL	0.01%
10.	ASCORBYL PALMITATE	0.01%
11.	CITRIC ACID	0.01%
12.	TOCOPHERYL ACETATE	1.00%
13.	PURIFIED WATER	59.93%
14.	HYDROXYPROPYL CHITOSAN	1.00%

15.	XANTHAN GUM	1.00%
16.	DENATURATED ETHYL ALCOHOL	3.00%
17.	PHENETHYL ALCOHOL	1.00%
18.	CAPRYLYL GLYCOL	1.00%
19.	POTASSIUM AZELOYL DIGLYCINATE	1.00%

**Preparation**

[0031] The formulation was prepared by using the same method described for Example 1.

**Example 3**

[0032] An oil in water cream having the following w/w % composition was prepared:

1.	POTASSIUM PALMITOYL HYDROLYZED WHEAT PROTEIN	2.00%
2.	CETEARYL ALCOHOL	5.00%
3.	GLYCERYL STEARATE SE	3.00%
4.	DICAPRYLYL ETHER	5.00%
5.	ETHYLHEXYL METHOXYCINNAMATE	4.00%
6.	LECITHIN	0.04%
7.	ASCORBYL PALMITATE	0.01%
8.	CITRIC ACID	0.01%
9.	TOCOPHERYL ACETATE	1.00%
10.	PURIFIED WATER	72.94%
11.	HYDROXYPROPYL CHITOSAN	1.00%
12.	XANTHAN GUM	1.00%
13.	DENATURATED ETHYL ALCOHOL	3.00%
14.	PHENETHYL ALCOHOL	1.00%
15.	POTASSIUM AZELOYL DIGLYCINATE	1.00%

**Preparation****[0033]**

Phase A: Hydroxypropyl chitosan was dispersed in ca. 50%wt of total water until a clear solution was obtained. The solution was heated at  $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and Xanthan gum was added and stirred until a homogenous solution was obtained.

Phase B: Potassium palmitoyl, Cetearyl Alcohol, Glyceryl Stearate SE, Dicaprylyl Ether, Ethylehexyl methoxycinnamate, Lecithin, Ascorbyl Palmitate, Citric Acid and Tocopheryl Acetate were mixed together and heated at  $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$ .

[0034] Phase B was added to Phase A under agitation (turbo) to allow the emulsification. The resulting emulsion was cooled to  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  under continuous mixing.

[0035] Phenethyl Alcohol, Potassium Azeloyl Diglycinate dissolved in the rest of purified water (50%wt) and Ethyl Alcohol were mixed into the emulsion at the end of preparation. The product was kept under gentle agitation until a homogenous oil in water cream was obtained.

**Example 4**

[0036] An oil in water cream having the following w/w % composition was prepared:

1.	POTASSIUM PALMITOYL HYDROLYZED WHEAT PROTEIN	2.00%
2.	GLYCERYL STEARATE	4.00%
3.	CETEARYL ALCOHOL	4.00%
4.	GLYCERYL STEARATE SE	2.00%
5.	DICAPRYLYL ETHER	5.00%
6.	ETHYLHEXYL METHOXYCINNAMATE	8.00%
7.	BUTYL METHOXYDIBENZOYLMETHANE	2.00%
8.	BIS-ETHYLHEXYLOXYPHENOL METHOXYPHENYL TRIAZINE	3.00%
9.	LECITHIN	0.040%
10.	TOCOPHEROL	0.002%
11.	ASCORBYL PALMITATE	0.002%
12.	CITRIC ACID	0.002%
13.	TOCOPHERYL ACETATE	0.20%
14.	HYDROXYPROPYL CHITOSAN	1.00%
15.	XANTHAN GUM	0.30%
16.	DENATURATED ETHYL ALCOHOL	2.00%
17.	PHENETHYL ALCOHOL	0.50%
18.	CAPRYLYL GLYCOL	0.50%
19.	POTASSIUM AZELOYL DIGLYCINATE	0.50%
20.	PURIFIED WATER q.s to	100.00%

**Preparation**

[0037] The preparation was made as in Example 1. A homogenous oil in water cream was obtained.

**Example 5**

[0038] A comparative evaluation of the inhibition of VEGF (Vascular Endothelial Growth Factor) release on human 3D artificial skin was tested by the preparation as per the Example 4, compared to two different preparations, respectively named LPOL2899A (same as per the Example 4, but not containing POTASSIUM AZELOYL DIGLYCINATE), LPOL2899B (same as per the Example 4, but not containing HYDROXYPROPYL CHITOSAN) and LPOL2899C (same as per the Example 4, but not containing either POTASSIUM AZELOYL DIGLYCINATE or HYDROXYPROPYL CHITOSAN).

[0039] The effect of the four preparations was tested on the inhibition of Vascular Endothelial Growth Factor (VEGF) production induced by a pro-inflammatory stimulus on 3D human epidermis. VEGF is a strong angiogenic protein that significantly influences the vessels permeability and is constitutively expressed in keratinocytes, i.e. the cells of the skin. Under stressful conditions, such as exposure to soluble inflammation mediator like IL-1 alpha, epidermal keratinocytes increase the synthesis and release of VEGF. Epidermis units have been treated with IL-1 $\alpha$  in the cell medium to induce an increase in the VEGF synthesis, and at the same time treated applying the investigated samples undiluted on the epidermis corneous layer. Following 24 h treatment, the cell culture medium below the epidermis units was collected and analyzed for the VEGF content through an ELISA assay.

[0040] The tested samples were the preparation as per the Example 4 and the two comparative preparations LPOL2899A and LPOL2899B. Skin units treated with IL-1 $\alpha$  only have been used as positive controls. The experiment was carried out in three



replicas.

[0041] *In vitro* test system employed consists of a tridimensional artificial system of human epidermis (Mattek, USA) i. e. a reconstructed artificial human skin model comprising normal human epidermal keratinocytes, growing as an integrated three-dimensional cell culture model, perfectly mimicking the human skin *in vitro*. The model exhibits normal barrier functions (presence of a differentiated stratum corneum).

[0042] About 20 mg of each undiluted sample have been applied on epidermis unit in three replicas, the exposure 30' following the products application, epidermis units, except the controls, have been treated for 2 h with 500 pg/ml of IL-1 $\alpha$  (Prospec) in the cell medium, to improve the VEGF synthesis.

[0043] After 2 h the cel medium has been removed and changed. The incubation of the samples has been carried up to 24 hours at 37°C, 5% CO<sub>2</sub>.

[0044] As positive control epidermis units treated with IL-1  $\alpha$  only have been used. At the end of the exposure period, the products were removed, the tissue gently washed with phosphate buffer (PBS) for further MTT and viability assay, and the culture medium have been collected for VEGF assay.

[0045] VEGF release assay following IL-1 $\alpha$  treatment, 500 pg/ml, with and without treatment with the samples is reported in the following table.

Sample	VEGF pg/ml (DS%)	% inhibition
Preparation of Example 4 + 500pg/ml IL-1 $\alpha$	313,21 (26,9)	<b>46,4</b>
LPOL 2899A + 500pg/ml IL-1 $\alpha$	386,03 (4,6)	<b>33,9</b>
LPOL 2899B + 500pg/ml IL-1 $\alpha$	433,86 (6,9)	<b>25,7</b>
LPOL 2899C + IL-1 $\alpha$	477,25 (4,1)	<b>18,3</b>
500pg/ml IL-1 $\alpha$ (positive control)	583,93 (7,5)	———

[0046] The preparation containing the vehicle, but not the two ingredients potassium azeloyl diglycinate and hydroxypropyl chitosan, inhibited the IL-1  $\alpha$  induced VEGF release by only 18%. the effect of the preparation containing hydroxypropyl chitosan was 25.7% inhibition and that of the preparation containing potassium azeloyl diglycinate was 33.9% inhibition. The preparation as per the Example 4 had the strongest inhibitory effect (46.4% inhibition) confirming a synergistic activity of the two components on the protection of skin against the insult of IL-1  $\alpha$ .

## REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- WO02057983A [0009]
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**Patentkrav****1. Sammensætning indeholdende:**

(A) mindst chitosan, hydroxyalkylchitosan og/eller et fysiologisk acceptabelt salt deraf, og;

5 (B) mindst lineær og/eller alkyl C<sub>6</sub>-C<sub>12</sub>-dicarboxylsyreamid og/eller et fysiologisk acceptabelt salt deraf.

**2. Sammensætning ifølge krav 1, kendetegnet ved at** hydroxyalkylchitosanen er vandopløselig.

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**3. Sammensætning ifølge krav 1, kendetegnet ved at** hydroxyalkylchitosanen er hydroxypropylchitosan.

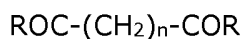
**4. Sammensætning ifølge krav 1, kendetegnet ved at** det fysiologisk acceptable  
15 salt af chitosanen, hydroxyalkylchitosan og/eller C<sub>6</sub>-C<sub>12</sub>-dicarboxylsyreamid er et natrium- og/eller kaliumsalt.

**5. Sammensætning ifølge krav 1, kendetegnet ved at** C<sub>6</sub>-C<sub>12</sub>-dicarboxylsyren er en C<sub>8</sub>-C<sub>10</sub>-dicarboxylsyre, fortrinsvis en C<sub>9</sub>-dicarboxylsyre.

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**6. Sammensætning ifølge krav 1, kendetegnet ved at** dicarboxylsyren er azelasyre.

**7. Sammensætning ifølge krav 1, kendetegnet ved at** C<sub>6</sub>-C<sub>12</sub>-  
25 dicarboxylsyreamiden har følgende formel:



hvor:

30 • n består af mellem 4 og 10, fortrinsvis mellem 6 og 8 og, mere foretrukket, er den 7;

- R er en  $-N(R')(R'')$ -gruppe, hvor:
- R' er H eller en C<sub>1</sub>-C<sub>4</sub>-alkylgruppe, og
- R'' er H, en C<sub>1</sub>-C<sub>4</sub>-alkylgruppe eller en C<sub>1</sub>-C<sub>4</sub>-carboxygruppe.

- 5 **8.** Sammensætning ifølge krav 7, **kendetegnet ved at** C<sub>1</sub>-C<sub>4</sub>-alkylgruppen er methyl og/eller ethyl og C<sub>1</sub>-C<sub>4</sub>-carboxygruppen er carboxymethyl.
- 9.** Sammensætning ifølge krav 1, **kendetegnet ved at** C<sub>6</sub>-C<sub>12</sub>-dicarboxylsyreamidet er azeloyldiglycin.
- 10 **10.** Sammensætning ifølge krav 1, **kendetegnet ved at** C<sub>6</sub>-C<sub>12</sub>-dicarboxylsyreamidsaltet er kaliumazeloyldiglycinat.
- 11.** Sammensætning ifølge krav 1, **kendetegnet ved at** komponent (A) er til
- 15 stede i mængder på fra 0,1 til 10%, fortrinsvis fra 0,2 til 5%, mere foretrukket fra 0,25 til 2,0%, i forhold til vægten af hele sammensætningen.
- 12.** Sammensætning ifølge krav 1, **kendetegnet ved at** komponent (B) er til
- 20 stede i mængder på fra 0,1 til 30%, fortrinsvis fra 0,25 til 25%, mere foretrukket fra 0,5 til 20 vægtprocent, i forhold til vægten af hele sammensætningen.
- 13.** Sammensætning ifølge krav 1, **kendetegnet ved at** være i flydende, halvflydende eller halvfast form, herunder opløsning, suspension, lotion, emulsion, kolloid, creme eller gel.
- 25 **14.** Sammensætning ifølge krav 1, **kendetegnet ved at** indeholde farmaceutisk og/eller kosmetisk acceptable aktive bestanddele, excipienser, adjuvanter og/eller bærere.
- 30 **15.** Sammensætning ifølge et hvilket som helst af kravene 1 til 14, til anvendelse i behandlingen og/eller forebyggelse af rosacea.

**16.** Sammensætning ifølge et hvilket som helst af kravene 1 til 14, til anvendelse i behandlingen og/eller forebyggelse af teleangectasia, fortrinsvis ben-teleangectasia.

5 **17.** Sammensætning ifølge et hvilket som helst af kravene 1 til 14, til anvendelse i behandlingen og/eller forebyggelse af couperose.