(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

(10) International Publication Number
WO 02/060405 A1


(21) International Application Number: PCT/EP01/01019

(22) International Filing Date: 29 January 2001 (29.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): COSMOFERM B.V. [NL/NL]; Wateringseweg 1, NL-2600 MA Delft (NL).

(72) Inventors: and

(74) Agent: LUYS, Marie-José; Gevers & Vander Haeghen, Rue de Livourne, 7, B-1060 Brussels (BE).

(54) Title: VETERINARY DERMATOLOGIC COMPOSITION COMPRISING A SPHINGOID BASE AND/OR A SPHINGOID BASE DERIVATIVE

(57) Abstract: This invention relates to a veterinary dermatological composition suitable for topical application, the composition containing as an active compound an amount of a sphingoid base, a shingoid base derivative or a mixture of two or more of these compounds.


Published: — with international search report

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VETERINARY DERMATOLOGICAL COMPOSITION COMPRISING A SPHINGOID BASE AND/OR A SPHINGOID BASE DERIVATIVE

Field of the invention.

The present invention relates to a veterinary dermatologic composition.

Background of the invention.

The skin of a living being constitutes a barrier to the environment which is capable of adapting itself to varying environmental conditions. Besides forming a structural barrier to the environment, the skin plays an important physiological role in that it provides physical protection, assists in the thermal regulation of the organism and has a metabolic, sensorial and storage function. The physical barrier function of the skin is mainly provided by the outermost lipid layer or stratum corneum. The ceramides present in the stratum corneum, which mainly result from enzymatic deglycosylation of cerebrosides, provide protective properties and form a permeable lipid filter, in particular a hydrophobic barrier, towards the environment.

Besides this physical barrier, the skin also provides a chemical barrier function in that the skin surface is colonised by a wide variety of micro-organisms that assist in maintaining a natural equilibrium of the skin. However, due to a.o. environmental factors and contact of the skin with cleansing or other products, this natural equilibrium may get disturbed, involve an uncontrollable outgrowth of certain micro-organisms within the skin microflora and the consequential impaired lipid barrier function and dermatologic infections.
It has been found in the recent years that also with animals, in particular furry animals, domestic animals as well as farm animals, the number of cutaneous infections where over-populations of micro-organisms intervene, is severely increasing. Most probably this problem must be associated with the changing living conditions of the animals, the occurrence of bacterial and fungal overpopulation and a consequential weakening of the fur. The malfunctioning of the cutaneous barrier may in turn involve various immunologic reactions, in particular an increased microbial and fungal sensitivity, bacterial proliferation, pilar anomalies and inflammatory responses. In particular, the occurrence of primitive infections, dermatoses over-infections and parasitoses has been more frequently observed. Dermatoses and parasitoses often involve with the animal a reaction of intensive scratching due to which the distortion of the ecoflora of the fur may be further aggravated. Also an additional source of lesions in the skin and fur, inflammatory reactions and keratinisation problems may be created, which in the end will adversely affect the over-all health of the animal.

The observed increase of the occurrence of primitive infections, dermatoses over-infections and parasitoses thus obviates the need to a dermatological composition and medicament, which are suitable for use on animal skin and fur, provide anti-microbial and anti-fungal activity in particular anti-yeast activity and anti-inflammatory activity, and are capable of positively interfering in keratinisation problems occurring with the animal.

**State of the art.**

From WO 98/49999 it is known that sphingoid base containing formulations show growth-inhibitory activity against gram-negative as well as against gram-positive bacteria on the human skin, when present in a concentration of at least 0.005 wt. %. Antimicrobial activity of sphingoid bases has been found against bacteria, yeasts and
fungi. Typical applications include treatment of acne, dandruff, mycoses, i.e. cosmetic and/or dermatological applications on human skin and hair.

In FR-A-2.679.770 dispersions of a ceramide and/or glycoceramide in specific surface active agents are disclosed for use as e.g. a shampoo or rinsing agent with which disentangling of hair may be facilitated. The surface active agents disclosed include quaternary ammonium salts and halogenated tetra-alkyl ammonium compounds.

In EP-B-720.847 shampoo, skin or hair care compositions containing Ceramide 6 are disclosed. It is explained that ceramide 6 would be capable of reducing escape of water from keratinous fibres.

However, none of the aforementioned publications of the state of the art addresses the use of sphingoid bases in veterinary dermatological compositions suitable for topical application.

It is now the aim of the present invention to provide a dermatological composition suitable for use on animal skin and fur, capable of showing anti-microbial and anti-fungal activity.

**Description of the invention.**

This is achieved with the present invention in that the veterinary dermatological composition contains as an active compound an amount of a sphingoid base, a sphingoid base derivative, a salt of a sphingoid base or a mixture of two or more of these compounds.

Depending on the adjuvants contained in the composition, the application field of the composition may vary from a preventive point of view, for example a hygienic composition which assists in restoring the barrier function of the skin and regulates the microbial population of the skin, to a curative point of view in an advanced dermatologic product, a veterinary medicament or as a complementary product to other medicaments.
The animal skin differs from the human skin mainly by the presence of a dense coat of hair which plays an essential role in the protection of the homeostatic equilibrium. It has now been found that the veterinary compositions of this invention are not only capable of showing anti-microbial and anti-fungal activity to a fur coated skin, but also that they are capable of preventing or regulating microbial over-population of the animal skin and fur. Without wanting to be bound by any theory, it is believed that the effect of the active compound of this invention can be explained by two synergistic effects. As the presence of a dense coat of hair on the animal skin constitutes a focus for the growth of micro-organisms, there is an increased risk to the occurrence of infections. The composition of this invention interferes herein in that due to its anti-microbial properties, the overpopulation of micro-organisms not only on the animal skin but also in the animal hair or fur may be counteracted. A first effect is thus to be found in the fact that with the composition of this invention, the ecoflora of the animal fur and thus the risk to the occurrence of infections, can be controlled. Besides this, the active compound of this invention has been found capable of enhancing recovery of the animal skin when irritated, inflamed or in case of lesions, and of improving vertical cohesion of skin cells as a result of which skin irritation and the tendency to scratching are counteracted. The composition thus shows a dual action, with which both the micro-organism population of the skin and fur may be controlled and the recovery capacity of the skin may be enhanced and in the end the over-all health of the animal will be improved.

Up to now, skin and fur problems with animals were largely ignored. Nowadays however, owners of animals have become more and more demanding thus stressing the need to provide veterinary compositions capable of preventing and treating those problems. Although the use of sphingo-lipids in compositions for application to the human skin and hair has been reported, there is no indication at all that in the prior art
that sphingoid bases, their derivatives or salts would be capable showing one or more of the above described effects with animal fur.

The type of sphingoid base used in the composition of this invention is not critical to the invention. The sphingoid base is preferably selected from the group of sphingosine, sphinganine and phytosphingosine, although phytosphingosine is preferred.

The sphingoid base used in the veterinary composition of this invention may be obtained from any suitable source, it may for example originate from a natural source, but preferably it is synthesised through a chemical process or fermentation process. To allow controlling the price of the veterinary composition, it is desirable that a sphingosine is used which is obtainable in reasonable amounts at commercially feasible costs. Chemically synthesised sphingoid base appears to be somewhat expensive as it is difficult to obtain the desired stereochemical configuration. Animal or vegetal sphingoid base can be obtained from extraction followed by purification of animal and vegetal tissue. Besides the fact that this is an expensive production route, animal sources are believed to be somewhat unsafe due to the regular occurrence of infections that are dangerous to man kind. Therefore, the sphingoid base used in the present invention is preferably obtained from a microbial fermentation process. More preferably it is obtained from a yeast, in particular *Pichia ciferii* as the thus obtainable phytosphingosine has been found to resemble animal skin in the best way. In a preferred embodiment of the invention, phytosphingosine is used as the sphingoid base which is obtained from *Pichia ciferii*-derived tetra-acetyl-phytosphingosine (TAPS), through deacetylation. The deacetylation reaction may be a chemical reaction, for example an alkali catalysed hydrolysis in the presence of KOH, or may be an enzymatic reaction. To obtain a phytosphingosine with a high purity, it may be desirably to subject the phytosphingosine resulting
from the hydrolysis reaction to a purification step. Thereto any purification method known to the man skilled in the art may be used.

Suitable examples of sphingoid base derivatives include N-lactyl-phytosphingosine, N-salicyloyl-phytosphingosine, N-retinoyl-phytosphingosine, i.e. compounds which are N-substituted.

When referring to veterinary compositions comprising the salt of a sphingoid base, the anion of the salt may be derived from any suitable acid, i.e. those acids which upon mixing with the sphingoid base in a suitable solid produce a slat with an improved water solubility. The acids which itself are effective when applied to fur or skin are preferred. Preferred salts of the sphingoid base for use in the composition of this invention are the salts obtainable with those acids which upon mixing with the above mentioned sphingoid base in a suitable solvent, produce a salt with an increased water solubility as compared to the water solubility of the sphingoid base as such. The salts of phytosphingosine are preferred for better solubility and better bioavailability.

In one embodiment the acid is a hydrophilic acid capable of delivering the sphingoid base salt to the water phase of the veterinary composition. Suitable hydrophilic acids include α-hydroxy alkanoic acid, a β-hydroxy alkanoic acid, an α,β-dihydroxy alkanoid acid, an alkanedioic acid or a mineral acid. Examples of preferred hydrophylic organic acids are lactic acid, glycolic acid, malic acid, pyruvic acid, succinic acid, fumaric acid, ascorbic acid, gluconic acid and/or pyrog glutamic acid. Examples of preferred mineral acids are hydrochloric acid, nitric acid and/or phosphoric acid.

In another preferred embodiment, the acid is a lipophilic organic acid to allow increasing both the efficacy of the lipophilic acid and the sphingoid base in the sphingoid base salt.
In general, the sphingoid base salts will be prepared prior to their inclusion in the veterinary composition, as the inclusion in the veterinary composition of the sphingoid base as such and one or more of the above described acids will in general not result in an increased efficacy. A preferred process for preparing the sphingoid base salts of this invention is described in WO 00/53568 which is here incorporated by reference.

The inventor has further found that an effective doses of a veterinary composition will usually contain 1-500 mg of the active sphingoid base compound. The posology will usually be adapted to the phenomenon to be treated and the characteristics of the animal, e.g. type of animal, animal weight, age etc. In case of animals with a weight between approximately 5-50 kg such as for example domestic animals, usually two administrations per day will suffice when treating a disorder. For preventive treatment purposes one or a few administrations per week will most often be sufficient. The frequency and dose may however be adapted to the specific type of animal.

Preferred concentrations of the active compound in the veterinary dermatological composition of this invention preferably range from 0.01-20 wt. % of the active compound. The preferred concentration will usually be adapted to the type of application envisaged. More preferred concentrations may vary from 0.02 wt% to 10 wt. %, or 0.5-5 wt. %. Compositions intended for treating disorders will typically contain a higher amount of active compound than compositions intended for preventive use, e.g. normalisation of the flora of the fur and/or skin. Compositions intended for regulating the desquamative condition or controlling sur-populations of micro-organisms or fungicides will most often contain 0.05-5 wt. % of the veterinary composition of this invention.

To allow curing specific or severe distortions, the veterinary composition of this invention may contain one or more
compounds capable of improving the targeting to the location to be treated or the efficacy or having complementary activity to the active compounds of this invention. Examples of such compounds include (pseudo-) ceramides, preferably skin-identical ceramides, alpha-hydroxy acids for example lactic acid, citric acid, glycolic acid, beta-hydroxy acids for example salicylic acid, and derivatives of the afore mentioned hydroxy-acids, cytokines, anti inflammatory steroids and non-steroids, vitamine A, C, D, E, PP, biotine and B-type vitamines, hormones, benzoyl peroxide, various emollients, ureum, reductants, anti moth agents, antibiotics, anti-fungal agents, disinfectants and any other compounds with complementary activity known to the man skilled in the art.

The veterinary composition of this invention may further comprise an amount of one or more suitable adjuvants and/or formulation additives to render the composition suitable for application in the selected mode of administration of the veterinary composition, to assist in delivering the active compound to the required site, if so desired assist in dispersing the active compound over the complete epidermal surface and to allow the active compound to be maintained in an active condition for a period sufficiently long to prevent repetition of the distortion. In particular the veterinary compositions of this invention may contain one or more solvents, preferably water, an emollient for example a fat or an oil, or emulsions in which a mixture of water and fat or oil are used as solvent. Other suitable adjuvants include amongst others known to the man skilled in the art, gelling agents, softening agents, emulsifying agents, surfactants, preservatives.

The surfactant for use with the veterinary composition of this invention is preferably selected from the group of ionic surfactants, anionic and/or cationic surfactants, and non-ionic surfactants. Preferably the surfactant is selected from the group of betaines,
ethoxylated sorbitan esters for example Tween 80, laureth sulphate or glycol distearate for example Texapon® or Sinnoflor®.

The concentration of the surfactant will mostly vary from 0.01-10 wt. %, preferably from 0.1-5 wt. % or 0.5-2.5 wt. %.

Suitable gelling agents include polyacrylamides for example Carbopol®, acrylate/acrylic acid copolymers for example Aculyn®, acrylamide/acrylamido acid propane sulfite, cellulose derivatives, e.g. hydroxypropylcellulose and Klucel®, vegetal muco-polysaccharides, waxes e.g. bee wax, natural gums e.g. xanthane gum.

Examples of suitable emulsifying agents are those known to the man skilled in the art of veterinary products, for example sorbitan ester polysorbate, sorbitan stearate or laurate, stearic acid derivatives, propylene glycol stearate, polyethylene glycol steareth, a steareth or a ceteareth. In case the composition of this invention is formulated as an emulsion, the emulsion is preferably a submicron emulsion the particle size of which is preferably between 50-200 μm. Such emulsions may be applied in the usual manner, for example by spraying, aerosol.

Suitable softening agents include fatty alcohols or esters, isostearyl alcohol based products, sorbitol-polysaccharides for example Soothex®, Rhamnosoft®.

The veterinary compositions of this invention may be applied in the form of a shampoo, foaming baths, spray, spot on, lotion, gels, emulsion, or other forms of application known to the man skilled in the art may also be used. A spray will mostly be used in curative application, whereas a shampoo mostly will have a cleaning and preventive function and a lotion is especially suitable for cleaning of exsudative lesions and ensures a major antiseptic action without distorting the microflora of the fur.
Although the composition of this invention may contain one or more preservatives, the presence thereof may be omitted without this adversely affecting the stability of the composition. It is thus possible to prepare veterinary dermatologic compositions which are free of purposely added preservatives. Although there is no need to include preservatives, they may be incorporated if the circumstances so require or favour. Suitable preservatives include methyl p-hydroxy-benzoate (methylparaben), propyl p-hydroxy-benzoate (propylparaben), Hinokitiol®.

Application of the veterinary composition to animals with varying kinds of distortions, has evidenced that the active compounds of this invention present properties which have not been disclosed in or could not be expected from scientific or patent publications, nor from any results obtained when applied to the human skin.

In this respect, it has been experimentally evidenced for the first time that phytosphingosin shows anti-microbial activity against specific types of animal staphylocoques. It has been surprisingly found that the multiplication of Staphylococcus Intermedius cultures may be partly inhibited by administering 5 ppm of phytosphingosine or its hydrochloric acid salt and completely inhibited by administering 10 ppm of phytosphingosine or its hydrochloric acid salt. Experiments were carried out using doses of 0, 5, 10, 25, 50 and 100 ppm of phytosphingosine and its hydrochloric acid salt on Staphylococcus Intermedius in usual culture environment without solubilising agent.

Preliminary clinical experiments, in-vitro mycologic studies have evidenced anti-fungal action of phytosphingosine against Malassezia pachydermatitis, which is a frequently occurring distortion in the animal race as well as a regulating and corrective action to distorted cutaneous ecoflora of pet animals such as cats and dogs.

The experiments have shown that the veterinary composition of this invention allows to simultaneously assist in curing
inflammatory phenomena as well as solving primitive or secondary keratinisation problems. These effects are obviated by for example an over-all improvement of the quality of the fur, the smell, pruritus and desquamation.

A comparative study has been carried out to a group of seven dogs which showed a pathological fur: 4 dogs with DAPP, (atopic dermatitis) due to flea bites, one of which is associated with chronic seborreic dermatitis, two dogs showed atopi and one dog showed seborrhea. All dogs were treated with the composition of this invention in the shape of a foam, once a day for a period of 3 days, followed by two applications per week for three weeks.

The results obtained when treating DAPP with a medicament based on an association of the composition of this invention with fipronil (Frontline®) have been compared with the results obtained with a medicament based on an association of fipronil with anti-inflammatory non-steroid. In another study the effect to atopy has been evaluated of a treatment with an antiseptic foaming base in combination with a corticoid (beta-methason) on the one hand and a treatment with the veterinary composition of this invention.

The above disclosed experiments have evidenced that with the veterinary composition of this invention an important improvement can be obtained of the pruritus, inflammation and desquamation as compared to the known medicaments. When applied to the whole epidermal surface of the animal, the composition of this invention showed prolonged activity, thus allowing to prevent the occurrence of consequential distortions with the animal as well as distortions resulting from stress implied with the animal. Besides this, the veterinary compositions of this invention appear to show improved drying properties, easy to apply, provide excellent cleaning properties and excellent after -treatment properties.
The above described experiments have shown that the veterinary composition of this invention can be successfully used in hygienic products as well as in veterinary medicine, in particular with cats and dogs, for treating all inflammatory pathologies related to stress, parasitoses, dermatoses, atopic dermatitis, superinfection folliculites, modifications of the flora, contact eczema.

Shampoo or foaming bases containing the veterinary composition of this invention proved to be particularly suitable for preventing and correcting cutaneous problems associated with a proliferation of *Malassezia pachydermatis* or *Staphylococcus intermedius*. Emulsions, alcoholic lotions or sub-micronic emulsions are suitable for preventing fungal affections. When treating chronic superficial folliculites of a dog, when preventing of fungal affections preferably use is made of a gel or a micellar lotion which is adapted to cleaning exsudative lesions. Dermatoses or superinfections involved by *Staphylococcus intermedius* can be successfully treated with a cream.

The invention is further illustrated in the following examples.

**Example 1.**

A sub-micron lotion for spraying was prepared with the following composition (amounts given in parts by weight):

- phytosphingosine: 0.20
- isodecyl isononanoate: 15.00
- octyldodecanole: 10.00
- diethylhexylcyclohexane: 5.00
- squalane: 5.00
- butylene glycol: 3.00
- Quaternium 82: 2.00
- cetyl dimethicon copolyol: 1.50
isostearyl alcohol 0.50  
chlorphenesine 0.20  
conservatives 0.60  
water up to 100

5

Example 2.
A gel for topical application was prepared with the following composition (given in parts by weight)

10

Base gel
hydroxypropyl cellulose 3.30  
ethoxydiglycol 13.33  
ethanol 96° 83.34

15

Composition of the gel:
base gel 45.00  
ethanol 96° 27.30  
cyclomethicone 11.50  
alkylene lactate C12-C13 13.50  
isostearyl alcohol (Soothex ®) 2.50  
phytosphingosine 0.20

Example 3.
An emulsion for a foaming bases was prepared as known to the man skilled in the art, having the following composition (amounts given in parts by weight):

25

Phytosphingosine hydrochloric acid 0.25  
surfactant (Texapon ®) 64.00  
cyclomethicone 2.50
The dermatological composition of this invention is adapted for use in veterinary products and allows re-establishing of the animal ecoflora, preventing, correcting and treating of cutaneous phenomena with animals, which are related to problems occurring in the ecoflora, for example microbial or fungal surpopulation, or problems occurring in the pathologic development of a specific micro-organism. The dermatological composition of this invention in particular allows preventing and/or correcting inflammations related to specific parasitoses and dermatoses for example eczema, or originating from varying aggressions such as stress. The dermatologic composition of this invention is also suitable for use in the preparation of a veterinary medicament when treating inflammations which may result from varying aggressions, for example from stress or be related to specific parasitoses and dermatoses.

The compositions of this invention may be used in a more general manner to ensure regulation of the desquamative status, to control microbial and fungal surpopulations.
CLAIMS.

1. A veterinary dermatological composition suitable for topical application, characterised in that the composition contains as an active compound an amount of a sphingoid base, a sphingoid base derivative or a mixture of two or more of these compounds.

2. A veterinary dermatological composition as claimed in claim 1, characterised in that the active compound is a salt of phytosphingosine, in particular \( \alpha \)-hydroxy alkanolic acid, a \( \beta \)-hydroxy alkanolic acid, an \( \alpha,\beta \)-dihydroxy alkanoid acid, an alkanedioic acid, a mineral acid or a lipophilic organic acid.

3. A veterinary dermatological composition as claimed in claim 1 or 2, characterised in that as an active compound, use is made of a hydrochloric acid salt of phytosphingosine.

4. A veterinary dermatological composition as claimed in any one of claims 1-3, characterised in that the composition contains 0.01-20 wt. % of the active compound, preferably 0.1 - 5 wt. %.

5. A veterinary dermatological composition as claimed in any one of claims 1-4, characterised in that the composition comprises a compound capable of showing an effect complementary to the activity of the active compounds of this invention, selected from the group of alpha-hydroxy acids, lactic acid, citric acid, glycolic acid, beta-hydroxy acids, salicylic acid and derivatives of the afore mentioned hydroxy-acids, cytokines, anti inflammatory steroids and non-steroids, vitamine A, C, D, E, PP, biotine and B-type vitamines, hormones, benzoyl peroxide, various emollients, ureum, reductants, anti moth agents, antibiotics, anti-fungal agents, disinfectants.

6. A veterinary dermatological composition as claimed in any one of claims 1-5, characterised in that the composition is in the form of a shampoo, foaming base, spray, spot on, lotion, gel or emulsion of the active compound.
7. A veterinary dermatological composition as claimed in any one of claims 1-6, characterised in that a single dose of the composition contains 1-500 mg of the active compound.

8. A veterinary dermatological composition as claimed in any one of claims 1-7, characterised in that it is in the form of an emulsion with a mean particle size of between 50-200 nm.

9. Use of a sphingoid base, a derivative of a sphingoid base, a salt of a sphingoid base or a mixture of two or more of these compounds for manufacturing a veterinary medicament for use in anti-microbial, anti-fungal, anti-inflammation activity, inflammatory pathologies related to stress, parasitoses, dermatoses, atopic dermatitis, superinfection folliculites, modifications of the flora and/or contact eczema with animals.

10. Use of a sphingoid base for manufacturing a veterinary medicament for treating inflammations related to specific parasitoses and/or dermatoses or resulting from aggressions.

11. A veterinary pharmaceutical composition suitable for topical application, characterised in that the composition contains as an active compound an amount of a sphingoid base, a sphingoid base derivative, a salt of a sphingoid base or a mixture of two or more of these compounds.
A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48 A61K31/13

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)

IPC 7 A61K

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

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

EPO-Internal, PAJ, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search

15 August 2001

Date of mailing of the international search report

27/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Lelystad
Tel. (+31-70) 340-2040, Tx. 31 651 cpo NL, Fax: (+31-70) 340-3016

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