

Skin Protection and Anti-itching Formulation

Field of Invention

5 The present invention relates to a product for topical administration, preferably in the form of a cream, lotion or ointment. In particular, the present invention relates to a product for topical administration for use in the treatment of eczema and psoriasis and other related skin conditions. It may also be used to treat insect bites.

10 Background

The listing or discussion of a prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

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Itch is the major cause of morbidity and the most frequently encountered symptom in dermatology, especially in diseases characterized by a defective skin barrier.

Eczema, or dermatitis, is a group of skin conditions which can affect all age groups. The severity of eczema can vary. In mild forms, the skin is dry, hot and itchy, whilst in more severe forms, the skin can become broken and raw, and can bleed. There are many causes of eczema, which in part is because there are a number of different diseases covered by the term "eczema".

20 A prototypical example would be atopic dermatitis (AD), which affects 20% of children and 10% of adults. A study found that 87% of patients with AD experience pruritus on a daily basis, for a mean duration of 10 years. Atopic dermatitis, is thought to be a hereditary condition and it is believed that sufferers of atopic dermatitis are sensitive to allergens in the environment that are harmless to others. In other words, when a sufferer of atopic dermatitis is exposed to an allergen their immune system overreacts, leading to inflamed, irritated and sore skin. Associated atopic conditions include asthma and hay fever.

Another form of eczema is allergic contact dermatitis, which is caused by irritants such as chemicals and detergents and allergens such as nickel. As with atopic dermatitis, the body's immune system overreacts on coming into contact with an allergen and/or an irritant. The resulting allergic reaction often develops over a period of time. In other words, the severity

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of the resulting attack may increase through repeated contact with the substance giving rise to contact dermatitis.

Other forms of eczema include infantile seborrhoeic eczema, adult seborrhoeic eczema,
5 varicose eczema and discoid eczema.

Although there is currently no known cure for eczema, a number of treatments have been devised with a view to minimising the discomfort and distress associated with eczema. All of these treatment regimens begin with an effective skin care routine, all of which routines
10 make use of an emollient. Emollients are used to soften and smooth the scales of the skin, which help reduce rough, flaky skin and so help prevent the dryness normally associated with eczema. However, when the eczema cannot be suppressed by an emollient, it is standard practice to make use of a topical (or in very severe cases) an oral steroid. Problems associated with the above treatments are that the formulation may include
15 ingredients that may aggravate a subject's eczema or which may otherwise cause undesirable side-effects.

Psoriasis is an immune-mediated, genetic disease manifesting in the skin and/or joints. The most common type of psoriasis is plaque psoriasis in which patches of skin, called "lesions",
20 become inflamed and are covered by a silvery white scale. Psoriasis can be limited to a few lesions or it can involve moderate to large areas of skin. Other forms of psoriasis include guttate, characterised by small dot-like lesions; pustular, characterised by weeping lesions and intense scaling; inverse, characterised by intense inflammation; and erythrodermic, characterised by intense shedding and redness of the skin. The severity of psoriasis can
25 vary from person to person. As with eczema, although there are a number of treatments, both topical and systemic, utilised to manage the discomfort caused by the condition and clear psoriasis for periods of time, there is no known cure.

One of the symptoms associated with the condition of psoriasis is itching. One of the simplest ways to control this symptom is by keeping the skin moisturised, because dry skin
30 can induce and aggravate this symptom. To date, treatments to manage the condition of psoriasis include anti-histamines, steroids, topical antiseptics, topical immunomodulators, anti-depressants and aspirin. Again, these treatments may cause side effects or might make the condition worse due to the inclusion of ingredients that may exacerbate the condition.

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In addition to the above, various topical compositions have been released into the market that purport to reduce itching. One of these compositions is EucerinTM Skin Calming cream

which contains 0.1 wt% of menthol and may contains certain ingredients that may be harmful to a subject's skin. Dermacool™ comprises from 0.5 to 5 wt% menthol, but it is not a moisturiser and it contains paraffin, which is flammable. Aveeno™ skin relief soothing lotion contains some menthol, but it is flammable due to the inclusion of paraffin and it also
 5 includes oatmeal, which is a known sensitizing agent.

Thus, there is a need for new compositions and products that are topically administrable and can alleviate the distress and discomfort caused by eczema and psoriasis and other related skin conditions, including those with the symptoms of dry itchy skin and/or dry itchy
 10 lesions. It will be appreciated that any conditions that include itchiness may also benefit from such a composition.

Summary of Invention

15 The invention provides new compositions and products that can be administered topically to alleviate itching of the skin in a subject. Said itching may be a symptom caused by an insect bite, a plant or insect sting, and a pruritic skin disease

Thus, in a first aspect of the invention, there is provided a moisturising composition,
 20 comprising menthol, one or more ceramides and a dermatologically acceptable diluent or carrier, wherein menthol is present in an amount of from 0.1 wt% to 5 wt% of the entire composition and the one or more ceramides are present in an amount of from 0.0001 wt% to 5 wt% of the entire composition.

25 In embodiments of the first aspect of the invention:

(a) menthol may be present in an amount of from 0.5 wt% to 4 wt% and the one or more ceramides may be present in an amount of from 0.0008 wt% to 3 wt% (e.g. menthol may be present in an amount of from 1 wt% to 3.5 wt% and the one or more ceramides may be present in an amount of from 0.0008 wt% to 0.1 wt%, such as where menthol may be
 30 present in an amount of from 2 wt% to 3 wt% and the one or more ceramides may be present in an amount of from 0.0015 wt% to 0.0020 wt%);

(b) the one or more ceramides may be ceramide III;

(c) the weight to weight ratio of the menthol to the one or more ceramides may be from 1:1 to 5000:1 (e.g. from 10:1 to 3000:1 or from 1000:1 to 2500:1, such as 2000:1);

35 (d) the composition may further comprise at least one moisturising agent (e.g. selected from one or more of the group consisting of paraffin, filaggrin breakdown products, hydroxyethyl urea, fatty acids, fatty alcohols, hydrocarbon moisturisers, phospholipids,

polyhydric alcohols, sterols, vegetable waxes, wax esters, gelatin, glycerin, honey, hyaluronic acid, pantheol, propylene glycol, sodium or ammonium lactate, sodium pyrrolidine carboxylic acid, sorbital, urea, lanolin, an astringent emollient, a fattening emollient, and a protective emollient);

5 (e) the composition may further comprise an emulsifier (e.g. selected from one or more of the group consisting of anionic, cationic, and non-ionic emulsifiers (e.g. the emulsifier may be glyceryl stearate and/or PEG-100 stearate);

(f) the composition may further comprise a consistency-giving factor (e.g. selected from one or more of the group consisting of myristyl alcohol, cetyl alcohol, cetearyl alcohol and mixtures thereof (e.g. cetyl alcohol));

10 (g) the composition may further comprise one or more additives (e.g. selected from one or more of an anti-oxidant, a pH adjuster, a suspending agent, and a preservative).

In embodiments of the first aspect of the invention, or any technically sensible combination
15 of its embodiments above, the least one moisturising agent may be present in an amount of from 10 to 30 wt% (e.g. from 15 to 27 wt%); the emulsifier may be present in an amount of from 0.1 to 5 wt% (e.g. from 1.5 to 3.0 wt%); the consistency-giving factor may be present in an amount of from 0 to 5 wt% (e.g. from 1.5 to 3.0 wt%); the one or more additives may be present in an amount of from 0.1 to 3 wt% (e.g. from 1.0 to 2.0 wt%); and the diluent or
20 carrier may form the balance of the composition.

The moisturising composition in the above-mentioned aspect of the invention may be utilized in a method of medical treatment. Thus, according to further aspects of the invention, there is provided:

25 (a) a method of treating a condition or disorder presenting itching as a symptom in a subject, which method comprises applying an effective amount of the composition described in the first aspect of the invention, and any technically sensible combination of its embodiments, to an affected area of skin on the subject;

(b) use of the composition described in the first aspect of the invention, and any
30 technically sensible combination of its embodiments, for the manufacture of a medicament for the treatment of a condition or disorder presenting itching as a symptom in a subject;

(c) a composition according to the first aspect of the invention, and any technically sensible combination of its embodiments, for use in the treatment of a condition or disorder presenting itching as a symptom in a subject.

35 In the above aspects of the invention, the condition or disorder presenting itching as a symptom in a subject may be a condition or disorder that also has a skin barrier defect, for example a pruritic skin disease such as eczema and/or dry skin. In the above aspects of the

invention, the condition or disorder presenting itching as a symptom in a subject may be a condition selected from one or more of an insect bite, a plant or insect sting, and a pruritic skin disease. Examples of pruritic skin diseases that may be mentioned herein include, but are not limited to eczema and/or dry skin.

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Description

It has been surprisingly found that the combination of menthol and ceramides results in a clinically-effective treatment of itches that have a concurrent skin barrier defect. Without wishing to be bound by theory, it is believed that menthol may serve to suppress itch, while the ceramide(s) may serve to effectively treat the skin barrier defect. Addressing both symptoms concurrently and synergistically appears to more effectively treat conditions or diseases that present both symptoms.

Thus, the current invention relates to a product that may be used for any kind of itch, but may be particularly suited to treating itches that have a concurrent skin barrier defect, such as eczema and dry skin conditions. As such, there is disclosed a moisturising composition, comprising menthol, one or more ceramides and a dermatologically acceptable diluent or carrier, wherein menthol is present in an amount of from 0.1 wt% to 5 wt% of the entire composition and the one or more ceramides are present in an amount of from 0.0001 wt% to 5 wt% of the entire composition.

In embodiments herein, the word "comprising" may be interpreted as requiring the features mentioned, but not limiting the presence of other features. Alternatively, the word "comprising" may also relate to the situation where only the components/features listed are intended to be present (e.g. the word "comprising" may be replaced by the phrases "consists of" or "consists essentially of"). It is explicitly contemplated that both the broader and narrower interpretations can be applied to all aspects and embodiments of the present invention. In other words, the word "comprising" and synonyms thereof may be replaced by the phrase "consisting of" or the phrase "consists essentially of" or synonyms thereof and *vice versa*.

Moisturising is fundamental for the well-being of the skin and for the integral preservation of its intrinsic mechanical properties, which include elasticity, suppleness, plasticity and its protective function for the other tissues and organs of the body. Water is a significant component of the epidermis, which are the outermost layers of skin cells. One of the key functions of the epidermis is to generate the relatively-impermeable layer of dead or dying

skin cells known as the stratum corneum, which is the outermost layer of skin cells. In order to carry out its protective functions, the epidermis must be compact while remaining supple and it must shed the top layer of skin cells (i.e. the outermost layer of cells in the stratum corneum) at about the same rate as new skin cells are produced by the stratum basale - the innermost layer of the epidermis. A major stabilising element that helps to maintain the necessary balance between protection and shedding is the preservation of moisture in the stratum corneum. As such, when used herein, a "moisturising composition" refers to a composition that contains at least one component that may help to preserve moisture within the stratum corneum. This role may be achieved by one or more components within the composition, which may include the dermatologically acceptable diluent or carrier or the ceramides.

When used herein, the term "ceramides" refers to a molecule that is formed from sphingosine and a fatty acid. Any suitable ceramide may be used in the compositions disclosed herein. For example, suitable ceramides that may be used in the compositions of the current invention may be those described in The Merck Index, Thirteenth Edition, Budavari et al., Eds., Merck & Co., Inc., Rahway, N. J. (2001); the CTFA (Cosmetic, Toiletry, and Fragrance Association) International Cosmetic Ingredient Dictionary and Handbook, Tenth Edition (2004); "Safety Assessment of Ceramides as Used in Cosmetics", The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) (2015); and the "Inactive Ingredient Guide", U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of Management, January 1996. A particular ceramide that may be mentioned in embodiments of the invention is ceramide III (N-stearoyl-phytosphingosine).

It is noted that the stratum corneum is composed of 50% ceramides, 25% cholesterol, and 15% free fatty acids and that ceramides may act to moisturise the skin (Guillou, S. *et al.*, *International Journal of Cosmetic Science*. **33** (2): 138–143).

"Dermatologically acceptable diluent or carrier" means a carrier or diluent that may be applied topically to skin or keratinous tissue. The dermatologically acceptable diluent or carrier may be in a wide variety of forms such as, for example, simple solutions (water-based or oil-based), solid forms (gels or sticks), suspensions, gels, solids, liposomes (and other encapsulation technologies), and emulsions (such as water-in-oil or oil-in-water emulsions, and which may both include micro-emulsions and nano-emulsions). If in the form of an emulsion, the carrier may have a viscosity of from about 100 cps to about 200,000 cps using a Brookfield RVT viscometer.

Suitable dermatologically acceptable diluents or carriers that may be mentioned herein include water and/or water miscible solvents. The carrier may be present at an amount of from 1% to 99% by weight, based on the weight of the composition (e.g., from 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% to 90%). Suitable water miscible solvents include monohydric alcohols (e.g. having from 1 to 6 carbon atoms, such as ethanol and/or isopropanol), dihydric alcohols, polyhydric alcohols, glycerol, glycols, polyalkylene glycols such as polyethylene glycol, and mixtures thereof. When the composition is in the form of an emulsion, the water and/or water miscible solvents are typically associated with the aqueous phase of the emulsion. In some embodiments, the diluent or carrier may be, or include, a paraffinic substance such as C₁₃₋₁₄ isoparaffin. It will be appreciated that the above-mentioned diluents and carriers may also provide a moisturising effect in the moisturising composition of the current invention.

The composition of the current invention requires the inclusion of both menthol in an amount of from 0.1 wt% to 5 wt% (e.g. from 1 wt% to 5 wt%) and one or more ceramides in an amount of from 0.0001 wt% to 5 wt% of the entire composition. It is believed that the disclosed range of menthol in the composition allows for achieving significant itch relief, while minimizing the risk of inducing contact dermatitis.

Suitable weight percentages of menthol (relative to the weight of the entire composition) that may be disclosed herein include, but are not limited to from 0.5 wt% to 4 wt%, from 1 wt% to 3.5 wt% or from 2 wt% to 3 wt%. Suitable weight percentages of a ceramide(s) (relative to the weight of the entire composition) that may be disclosed herein include, but are not limited to from 0.0008 wt% to 3 wt%, from 0.0008 wt% to 0.1 wt% or from 0.0015 wt% to 0.0020 wt%. It will be appreciated that the weight percentage ranges of menthol and ceramides discussed herein may be mixed and matched in any suitable manner. Particular combinations of the amount of menthol and ceramides that may be mentioned herein include, menthol in an amount of from 0.5 wt% to 4 wt% and the one or more ceramides in an amount of from 0.0008 wt% to 3 wt%, such as menthol in an amount of from 1 wt% to 3.5 wt% and the ceramides in an amount of from 0.0008 wt% to 0.1 wt% (e.g. menthol in amount of from 2 wt% to 3 wt% and the ceramides in an amount of from 0.0015 wt% to 0.0020 wt%).

As the effects of the ceramides wear off over a period of time, it is an object of the current invention to seek a formulation where the effectiveness of the anti-itch effect wears off over time so that the formulation is reapplied on a regular basis. An advantage associated with this loss of anti-itching effectiveness over time is that it makes the subject reapply the

formulation at regular intervals and therefore obtain effective benefit from the skin barrier protection agents found within the formulation (e.g. ceramides). In certain embodiments of the invention that may be mentioned herein, the weight to weight ratio of the menthol to the one or more ceramides may be from 1:1 to 5000:1, such as from 10:1 to 3000:1, 1000:1 to 2500:1, or 2000:1.

Menthol may be used in any suitable form. For example, menthol may be derived from a synthetic or a natural source.

It will be appreciated that additional components may be present in the compositions described herein. Such additional components may include one or more of moisturising agents, emulsifiers, consistency-giving factors and other additives.

When used herein, a "moisturising agent" refers to any material that helps to increase the skin's hydration (water content) by reducing evaporation. As such, water itself is not a moisturising agent. A variety of these materials can be employed and each may be present at a level of from 0.01% to 15%, from 0.02% to 12%, from 0.05% to 10% by weight based on the weight of the composition. Suitable moisturising agents include, but are not limited to paraffins, filaggrin breakdown products, hydroxyethyl urea, fatty acids, fatty alcohols, hydrocarbon moisturisers, phospholipids, polyhydric alcohols (e.g. sorbitol, mannitol, xylitol, erythritol, glycerol, hexanetriol, butanetriol, propylene glycol, butylene glycol, hexylene glycol and the like), sterols, vegetable waxes, wax esters, gelatin, glycerin, honey, hyaluronic acid, pantheol, propylene glycol, sodium or ammonium lactate, sodium pyrrolidine carboxylic acid, sorbital, urea, lanolin, an astringent emollient, a fattening emollient, a protective emollient and mixtures thereof. Particular moisturising agents that may be mentioned herein include glycerine, hydroxyethyl urea, propylene glycol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, stearic acid, cyclopentasiloxane and phytosteryl/octyldodecyl lauroyl glutamate and combinations thereof, optionally all of these moisturising agents may be present in the composition, where each is present in an amount of from 0.05% to 10% by weight based on the weight of the composition.

For the avoidance of doubt, ceramides are not included in the weight percentage when calculating the amount of moisturising agent present in the composition.

As noted above, the moisturising composition may also include an emulsifier. An emulsifier may be desirable when the composition is provided in the form of an emulsion or if immiscible materials are being combined. The cosmetic compositions herein may include

from 0.05%, 0.1%, 0.2%, 0.3%, 0.5%, or 1% to 20%, 10%, 5%, 3%, 2%, or 1% emulsifier. Emulsifiers may be nonionic, anionic or cationic emulsifiers (e.g. surfactants). Non-limiting examples of emulsifiers are disclosed in McCutcheon's, Emulsifiers and Detergents, 2010 Annual Ed., published by M. C. Publishing Co. and in the Personal Care Product Council's
 5 International Cosmetic Ingredient Dictionary and Handbook, Thirteenth Edition, 2006, under the functional category of "Surfactants - Emulsifying Agents."

Suitable emulsifiers may include the following classes of ethers and esters: ethers of polyglycols and of fatty alcohols, esters of polyglycols and of fatty acids, ethers of
 10 polyglycols and of fatty alcohols which are glycosylated, esters of polyglycols and of fatty acids which are glycosylated, ethers of C₁₂₋₃₀ alcohols and of glycerol or of polyglycerol, esters of C₁₂₋₃₀ fatty acids and of glycerol or of polyglycerol, ethers of oxyalkylene-modified C₁₂₋₃₀ alcohols and of glycerol or polyglycerol, ethers of C₁₂₋₃₀ fatty alcohols and of sucrose or of glucose, esters of sucrose and of C₁₂₋₃₀ fatty acids, esters of pentaerythritol and of C₁₂₋₃₀
 15 fatty acids, esters of sorbitol and/or of sorbitan and of C₁₂₋₃₀ fatty acids, ethers of sorbitol and/or of sorbitan and of alkoxylated sorbitan, ethers of polyglycols and of cholesterol, esters of C₁₂₋₃₀ fatty acids and of alkoxylated ethers of sorbitol and/or sorbitan, and combinations thereof.

20 Linear- or branched-type silicone emulsifiers and emulsifying silicone elastomers may also be used. Suitable emulsifying silicone elastomers may include at least one polyalkyl ether or polyglycerolated unit.

Particular emulsifiers that may be mentioned herein include glyceryl stearate and PEG-100
 25 stearate.

In certain embodiments of the invention, the consistency-giving factor (also herein referred to as a wax) to be used in the composition may include, but is not limited to myristyl alcohol, cetyl alcohol, cetearyl alcohol and mixtures thereof. In particular embodiments of the
 30 invention that may be mentioned herein, the consistency-giving factor may be cetyl alcohol.

The compositions of the current invention may also further contain additives. Such additives may be selected from the group including anti-oxidants, pH adjusters, suspending agents, preservatives and combinations thereof.

35 Any suitable natural or synthetic antioxidants may be present in the moisturising composition of the present invention. Examples include tocopherol, Vitamin E derivatives, (e.g. Vitamin E

linoleate, Vitamin E, Vitamin E POE succinate, Vitamin E acetate), ascorbic acid, ascorbyl palmitate, ascorbyl-PMG, hydroxyacetophenone and combinations thereof. Antioxidants may be added to the composition in effective amounts to neutralize harmful oxidants, e.g. singlet oxygen. Typically, the antioxidant may be present in an amount of from about 0.1% to about 5% by weight, such as from about 0.2% to 0.5% by weight of the entire composition.

Compositions according to the present invention may also comprise preservatives. Preservatives can be either synthetic or natural. In certain embodiments, preservatives can be used to inhibit growth of undesirable microorganisms. Natural preservatives can include blackcurrant fruit extract, aspen bark, radish root, and sorbic acid, potassium sorbate, alone or in combination. Synthetic preservatives can include, for example, sodium hydroxymethylglycinate, tetrahexyldecyl ascorbate, tocopheryl acetate, ethylhexylglycerin, phenoxyethanol, methylparaben, ethylparaben, propylparaben, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, isothiazolinones, chlorinated aromatic compounds, para-hydroxybenzoic acids/parabens, alone or in combination. In particular embodiments that may be mentioned herein, the composition may include phenoxyethanol and/or ethylhexylglycerin. Other natural and synthetic preservatives can be found in the Cosmetic Handbook and Personal Care Products Council ingredient information. When present in the cosmetic composition, one or more preservatives can be included in an amount from about 0.001 wt% to about 5wt% of the entire composition, such as from about 0.08wt% to about 1.0wt% of the entire composition.

A pH adjusting agent may commonly be added to a moisturising composition to adjust the acidity of the composition to a desirable range, preferably to a pH of from 6 to 8. An example of a suitable pH adjusting agent is aminomethylpropanol. A pH adjusting agent may be added in an amount effective to change the pH of the composition to the desired pH range. Preferably, the pH adjusting agent is present in an amount that is less than 0.5 wt% of the total composition, such as from 0.01 to 1 wt% of the total composition.

A suspending agent can be added to the moisturising compositions disclosed herein to assist in suspending water-insoluble material in dispersed form throughout the moisturising composition. The suspending agent may be present at concentrations effective for modifying the viscosity of the cosmetic composition as desired for the final cosmetic product. Such concentrations can range from about 0.1wt% to about 5 wt% or from about 0.2wt% to about 2.0wt% of the composition. Suspending agents that may be useful in the current invention include, for example, crystalline suspending agents that can be categorized as acyl derivatives, long chain amine oxides, carbomers and mixtures thereof. Suspending agents

can also include, for example, ethylene glycol esters of fatty acids having from about 16 to about 22 carbon atoms, ethylene glycol stearates, mono- and distearate, preferably where the distearate contains less than about 7% of the mono-stearate, and combinations thereof. Other suspending agents can be found in the Cosmetic Handbook and Personal Care Products Council ingredient information.

In particular embodiments of the invention, at least one moisturising agent, an emulsifier, a consistency-giving factor and other additives (e.g. preservatives and suspending agents) may be present in the composition described herein. With that in mind, the composition may include from 10 to 30 wt% of at least one moisturising agent, from 0.1 to 5 wt% of an emulsifier, from 0 to 5 wt% of a consistency-giving factor and from 0.1 to 3 wt% of additives. In further embodiments of the invention, the composition may include from 15 to 27 wt% of at least one moisturising agent, from 1.5 to 3.0 wt% of an emulsifier, from 1.5 to 3.0 wt% of a consistency-giving factor and from 1.0 to 2.0 wt% of additives. It will be appreciated that, in addition to menthol and the ceramide(s), which may be present in any of the amounts stated above, that the balance of the composition is derived from the diluent or carrier.

The moisturising composition may be used in a method of medical treatment. Thus, the composition may be used in a method of treating a condition or disorder presenting itching as a symptom in a subject, which method comprises applying an effective amount of the compositions described herein to an affected area of skin on the subject. There is also provided a use of the composition described herein for the manufacture of a medicament for the treatment of a condition or disorder presenting itching as a symptom in a subject. In addition, the composition described herein is for use in the treatment of a condition or disorder presenting itching as a symptom in a subject.

The term "condition or disorder presenting itching as a symptom in a subject" may relate to a condition or disorder that also has a skin barrier defect, such as a pruritic skin disease (e.g. eczema and/or dry skin) or it may be an insect bite, a plant or insect sting.

The moisturising compositions of disclosed herein may be prepared according to conventional methods known in the art for making such compositions. Such methods may include mixing ingredients in one or more steps to achieve a relatively uniform state, with or without heating, cooling, application of vacuum, and the like. For example, emulsions may be prepared by first mixing the aqueous phase materials separately from the fatty phase materials and then combining the two phases as appropriate to yield the desired continuous phase. In certain embodiments, the compositions may be prepared to provide suitable

stability (physical stability, chemical stability, photostability, etc.) and/or delivery of active materials. The composition may be provided in a package sized to store a sufficient amount of the composition for a treatment period.

- 5 The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient (e.g. sufficient to treat or prevent the disease). The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).
- 10 For the avoidance of doubt, in the context of the present invention, the term "*treatment*" includes references to therapeutic treatment of patients in need of such treatment, as well as to the prophylactic treatment and/or diagnosis of patients which are susceptible to the relevant disease states.
- 15 The terms "*patient*" and "*patients*" include references to mammalian (e.g. human) patients. As used herein the terms "subject" or "patient" are well-recognized in the art, and, are used interchangeably herein to refer to a mammal, including dog, cat, rat, mouse, monkey, cow, horse, goat, sheep, pig, camel, and, most preferably, a human. In some embodiments, the subject is a subject in need of treatment or a subject with a disease or disorder. However, in
- 20 other embodiments, the subject can be a normal subject. The term does not denote a particular age or sex. Thus, adult and newborn subjects, whether male or female, are intended to be covered.

The aspects of the invention described herein (e.g. the above-mentioned compositions,

25 methods and uses) may have the advantage that, in the treatment of the conditions described herein, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have better selectivity over, have a broader range of activity than, be more potent than, produce fewer side effects than, or may have other useful pharmacological properties over, similar compounds, combinations, methods

30 (treatments) or uses known in the prior art for use in the treatment of those conditions or otherwise.

Further aspects and embodiments of the invention will now be described with respect to the following non-limiting examples.

Examples

Example 1

The ingredients used in a composition according to the current invention are provided below in Table 1.

No.	Ingredient	wt%	Functions
1	Water	64.43000	Diluent
2	Glycerin	10.00000	Humectant
3	Hydroxyethyl Urea	4.00000	Moisturising Agent
4	Propylene Glycol	3.00000	Humectant
5	Isopropyl Myristate	3.50000	Emollient
6	Menthol	3.00000	Itch Relief Agent
7	Glyceryl Stearate (and) PEG-100 Stearate	2.80000	Emulsifier/Moisturiser/Base
8	Cetyl Alcohol	2.50000	Consistency-giving factor
9	Stearic Acid	2.50000	Emollient/ Soap Base/Base
10	Cyclopentasiloxane	2.20000	Emollient
11	Phenoxyethanol Ethylehexylglycerin	0.91000 0.09000	Preservatives
12	Isostearyl Alcohol Ceramide III	0.48500 0.01500	Strengthen epidermal barrier and improve transepidermal water loss
13	Carbomer	0.25000	Suspending agent
14	Hydroxyacetophenone	0.20000	Anti-oxidant
15	Aminomethyl Propanol	0.07000	pH adjuster
16	Phytosteryl/Octyldodecyl Lauroyl Glutamate	0.05000	Emollient

Table 1

To a mixing tank was added, sequentially each ingredient from 1 to 16. After each addition, mixing was allowed to occur for five minutes before the next ingredient was added.

Example 2

Individuals, with or without skin problems, were invited to participate in a study. Subjects were instructed to apply the cream of Example 1 regularly at least twice daily for a month, over a total body surface area of at least 6%. The palm of the individual was used as a

reference for 1% of his or her body surface area. Subjects with skin diseases were informed to apply the cream over their dermatoses and also to continue their usual treatment.

Safety of application was assessed by the absence of the development of contact dermatitis or unpleasant cutaneous sensations induced by menthol. Contact dermatitis was defined in this analysis as the development of itch, pain and redness that prohibited further application.

Subjects were required to complete a written questionnaire 5 minutes, 1 week and 1 month after application. The questionnaire assessed if there was any itch, pain or redness after application. Subjects also reported their tolerability to the sensation induced by the cream. They were instructed to write down any other side effects and provide additional feedback. In addition, subjects with skin problems were required to grade the average intensity of itch experienced over the preceding week on a numerical scale of 1 to 10. This was to be assessed at baseline, 1 week and 1 month after application.

Change in pruritus scores from baseline to after 1 week and 1 month of application were assessed using the Wilcoxon signed rank test.

Results

A total of 60 volunteers were recruited, of whom 41 (68.3%) had no skin disease and 19 (31.7%) had self-reported pre-existing skin disease. The demographics of subjects with and without skin disease are shown in Table 2.

		Subjects without skin disease (n= 41)	Subjects with skin disease (n=19)
Age range, years		7 to 67	9 to 74
Male (%)		28 (68.3)	11 (57.9)
Ethnicity	Chinese	36 (87.8)	19 (100)
	Malay	2 (4.9)	0 (0)
	Indian	1 (2.4)	0 (0)
	Eurasian	1 (2.4)	0 (0)
	Caucasian	1 (2.4)	0 (0)

Table 2

In subjects without skin disease, 1 out of 41 (2.4%) stopped application after 1 week as the subject did not like the sensation induced by the cream. However, the subject used the cream subsequently to soothe sunburn with no adverse effects. Forty out of 41 subjects (97.6%) tolerated application of the cream and did not develop contact dermatitis. No other side effects were reported.

Of the 19 subjects with skin disease, 18 (94.7%) had eczema and 1 (5.3%) had epidermolysis bullosa pruriginosa. One subject with eczema stopped after the first application upon experiencing a stinging sensation. This subject, however, did not report any itch or redness. The remaining 18 subjects completed 1 month's application of the cream. All did not develop features of contact dermatitis except for 1 subject with neck eczema. After application, this subject developed mild itch (itch score of 1/10) in association with moderate pink coloration. These symptoms developed and resolved spontaneously within 15 minutes after every application. The itch score of this subject improved from 3/10 at baseline to 1/10 at 1 week and 1/10 at 1 month after regular application. There were otherwise no adverse effects reported by the subjects.

Seventeen out of 19 subjects (89.5%) had their itch scores analyzed. One subject had stopped after the first application and another had not filled in the itch scores. The mean itch score had improved from 4.3 at baseline to 2.9 at 1 week ($p < 0.01$) and 2.0 at 1 month ($p < 0.01$). In a subgroup analysis of 16 individuals with eczema, mean itch scores also improved from 4.1 at baseline to 2.7 at 1 week ($p = 0.01$) and 1.8 at 1 month ($p < 0.01$) (Table 3).

Average itch intensity over the preceding 1 week: itch score on a numerical scale (0-10)	Baseline	One week after cream application	One month after cream application
Mean $\pm$ SD	4.1 $\pm$ 2.7	2.7 $\pm$ 2.7	1.8 $\pm$ 2.3
p-value for test of difference from baseline*	NA	0.0129	0.0085

*Wilcoxon signed-rank test

Table 3

Discussion

This formulation seeks to address the intricately related problems of itch and skin barrier defects in many skin diseases, such as the various forms of eczema and asteatosis associated with advanced aging, renal disease, diabetes mellitus and human immunodeficiency virus infection.

When this formulation was used, it was observed that the fast onset of itch relief experienced from applying the cream provided subjects with a positive feedback to use the cream again. Although the anti-pruritic effect was temporary, with repeated application of the cream, the moisturizer base served to repair the underlying skin barrier defect and led to a more sustained relief from itch. Thus, the formulation was clinically effective in the management of pruritic dermatoses associated with skin barrier defect.

In conclusion, the results indicated that application of a 3% menthol-containing moisturising cream was safe in healthy individuals and individuals who reported to have eczema. In the latter, application of the cream led to a significant reduction in itch scores after 1 week and 1 month.

Claims

1. A moisturising composition, comprising menthol, one or more ceramides and a dermatologically acceptable diluent or carrier, wherein menthol is present in an amount of from 0.1 wt% to 5 wt% of the entire composition and the one or more ceramides are present in an amount of from 0.0001 wt% to 5 wt% of the entire composition.
2. The composition according to Claim 1, wherein menthol is present in an amount of from 0.5 wt% to 4 wt% and the one or more ceramides are present in an amount of from 0.0008 wt% to 3 wt%.
3. The composition according to Claim 2, wherein menthol is present in an amount of from 1 wt% to 3.5 wt% and the one or more ceramides are present in an amount of from 0.0008 wt% to 0.1 wt%.
4. The composition according to Claim 3, wherein menthol is present in an amount of from 2 wt% to 3 wt% and the one or more ceramides are present in an amount of from 0.0015 wt% to 0.0020 wt%.
5. The composition according to any one of the preceding claims, wherein the one or more ceramides is ceramide III.
6. The composition according to any one of the preceding claims, wherein the weight to weight ratio of the menthol to the one or more ceramides is from 1:1 to 5000:1.
7. The composition according to Claim 6, wherein the weight to weight ratio of the menthol to the one or more ceramides is from 10:1 to 3000:1.
8. The composition according to Claim 7, wherein the weight to weight ratio of the menthol to the one or more ceramides is from 1000:1 to 2500:1, such as 2000:1.
9. The composition according to any one of the preceding claims, wherein the composition further comprises:
 - at least one moisturising agent; and/or
 - an emulsifier; and/or
 - a consistency-giving factor; and/or
 - one or more additives.

10. The composition according to Claim 9, wherein:

the at least one moisturising agent is selected from one or more of the group consisting of paraffins, filaggrin breakdown products, hydroxyethyl urea, fatty acids, fatty alcohols, hydrocarbon moisturisers, phospholipids, polyhydric alcohols, sterols, vegetable waxes, wax esters, gelatin, glycerin, honey, hyaluronic acid, pantheol, propylene glycol, sodium or ammonium lactate, sodium pyrrolidine carboxylic acid, sorbital, urea, lanolin, an astringent emollient, a fattening emollient, and a protective emollient; and/or

the emulsifier is selected from one or more of the group consisting of anionic, cationic, and non-ionic emulsifiers; and/or

the consistency-giving factor is selected from one or more of the group consisting of myristyl alcohol, cetyl alcohol, cetearyl alcohol and mixtures thereof (e.g. cetyl alcohol); and/or

the one or more additives are selected from one or more of an anti-oxidant, a pH adjuster, a suspending agent, and a preservative.

11. The composition according to Claim 9 or Claim 10, wherein:

the least one moisturising agent may be present in an amount of from 10 to 30 wt%;

the emulsifier may be present in an amount of from 0.1 to 5 wt%;

the consistency-giving factor may be present in an amount of from 0 to 5 wt%;

the one or more additives may be present in an amount of from 0.1 to 3 wt%; and

the diluent or carrier forms the balance of the composition .

12. The composition according to Claim 11, wherein:

the least one moisturising agent is present in an amount of from 15 to 27 wt%;

the emulsifier is present in an amount of from 1.5 to 3.0 wt%;

the consistency-giving factor is present in an amount of from 1.5 to 3.0 wt%;

the one or more additives are present in an amount of from 1.0 to 2.0 wt%; and

the diluent or carrier forms the balance of the composition.

13. A method of treating a condition or disorder presenting itching as a symptom in a subject, which method comprises applying an effective amount of the composition described in any one of Claims 1 to 12 to an affected area of skin on the subject.

14. Use of a compound formula I for the manufacture of a medicament for the treatment of a condition or disorder presenting itching as a symptom in a subject.

15. A composition according to any one of Claims 1 to 12 for use in the treatment of a condition or disorder presenting itching as a symptom in a subject.

16. The method of Claim 13, the use of Claim 14 and the composition of Claim 15, wherein the condition or disorder presenting itching as a symptom in a subject is a condition or disorder that also has a skin barrier defect, optionally wherein the condition or disorder is a pruritic skin disease (e.g. eczema and/or dry skin).

17. The method of Claim 13, the use of Claim 14 and the composition of Claim 15, wherein the condition or disorder that also has a skin barrier defect is selected from one or more of an insect bite, a plant or insect sting, and a pruritic skin disease.