Abstract:

A61K 8/49 (2006.01) A61K 9/107 (2006.01) A61Q 19/00 (2006.01) A61K 31/4425 (2006.01)

Applicant: ALMIRALL, S.A. [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).


Agent: SRINIVASAN, Ravi Chandran; 14 South Square, Gray’s Inn, London Greater London WC1R 5J (GB).

Title: TOPOICAL PHARMACEUTICAL OR COSMETIC COMPOSITIONS COMPRISING OCTENIDINE DIHYDROCHLORIDE

Abstract: Topical pharmaceutical or cosmetic compositions are described comprising octenidine dihydrochloride. Said compositions are stable and can be safely and easily applied over large surface areas of the skin in an acceptable way by the general patient population for the treatment or prevention of some skin disorders or diseases.
TOPICAL PHARMACEUTICAL OR COSMETIC COMPOSITIONS COMPRISING OCTENIDINE DIHYDROCHLORIDE

FIELD OF THE INVENTION
The present invention relates to topical pharmaceutical or cosmetic compositions comprising octenidine dihydrochloride. The invention further relates to methods of treatment of some skin diseases or disorders by administering these compositions.

BACKGROUND OF THE INVENTION
'Atopy' is the term used for the tendency to develop eczema, asthma and/or hay fever. If a person has one of these conditions, they may be referred to as atopic.

The words 'eczema' and 'dermatitis' are interchangeable and mean the same thing.

Atopic eczema (or atopic dermatitis) is a dry, itchy inflammation of the skin. Atopic eczema can affect any part of the skin, including the face, but the areas most commonly affected are the bends of the elbows, around the knees, and around the wrists and neck. These are known as 'flexural' areas. The condition is usually very itchy and in some people it disturbs their sleep. It affects both sexes equally and usually starts in the first weeks or months of life. It is most common in children, although it can carry on into adult life or come back in the teenage or early adult years.

People with atopic eczema also have a tendency to dry skin, which makes them vulnerable to the drying effects of soaps (Williams et al., Atopic eczema, In: Evidence-based dermatology, BMJ Publishing Group, 2003, pp.144-218)

Bacterial or fungal infection, such as infection with Staphylococcus aureus, which is commonly found in all types of eczema, is a distinct aggravation factor for atopic eczema.

When atopic eczema flares, topical corticosteroid creams, lotions and ointments may be applied to the affected areas. Creams are usually the best option to treat moist or weeping areas of skin. Ointments are preferably used to treat areas of skin which are dry or thickened. Lotions may be useful to treat hairy areas such as the scalp.

The handling of S. aureus infected eczema can include two different strategies:
treatment of infected skin and prevention of colonization/infection in patients at risk.
The management of atopic eczema patients often includes the use of antiseptics to prevent colonization or reduce bacterial counts.
An antiseptic is a disinfectant (chemical agent which destroys or inhibits the growth of pathogenic micro-organisms in the non-sporing or vegetative state) which is used on skin and other living tissues thereby limiting or preventing infection (Martindale - The complete drug reference, 32nd edition, 1999, Disinfectants and Preservatives)

The main advantages of antiseptics are: that their potential to induce resistance in S. aureus even with repeated and widespread use seems to be very low; that different preparation are available to suit individual needs according to disease activity, and concomitant treatment; and that, in contrast to some topical antibiotics, they rarely cause delayed-type hypersensitivity. Antiseptics are normally used in the form of baths (such as sodium hypochlorite), in the form of antiseptic ointments (such as 1-2% triclosan or 0.5-1% chlorhexidine gluconate added to an emollient), or in the form of aqueous solutions (such as 0.1% octenidine dihydrochloride in combination with 2% of phenoxyethanol, or 4% chlorhexidine gluconate) (Schnopp C, Ring J, Mempel M., The role of antibacterial therapy in atopic eczema; Expert Opin. Pharmacother. 2010 Apr;11(6):929-36).

However, due to the chemical properties of some antiseptic agents such as chlorhexidine gluconate or octenidine dihydrochloride (cationic substances) the presence of surfactants in a formulation may interfere with the activity of said antiseptic agents (Sedlock et al., Microbicidal activity of octenidine hydrochloride, a new alkanediylbis[pyridine] germicidal agent, Antimicrob. Agents Chemother. 1985 December; 28(6): 786-790)

In the field of topical therapies for treating skin diseases or disorders, particularly in the treatment of infected eczema, cutaneous bacterial infections or cutaneous fungal infections, there is a need for topical compositions comprising antiseptic agents, in particular octenidine dihydrochloride, which are effective (provide disinfectant properties), chemically stable, free of side effects, cosmetically acceptable (in terms of texture, dispersion, permeation, etc.) and which can provide additional benefits to the skin such as improving the skin barrier and increasing the skin moisture. In addition, it would be desirable that the compositions would be able not only to treat the skin once it has been infected but also to prevent the colonization/infection of the skin in patients at risk, i.e. patients suffering from atopic dermatitis and/or dry skin.

Pharmaceutical and cosmetic compositions comprising octenidine dihydrochloride are known in the art. For instance, WO 2007/031520 describes pharmaceutical semisolid
preparations comprising octenidine dihydrochloride. In addition, none of the preparations described in WO 2007/031520 comprise 1-20 wt.% of at least one petroleum hydrocarbon and, simultaneously, 30-70 wt.% of water.

WO 2007/031519 describes antimicrobial preparations comprising octenidine dihydrochloride encapsulated in liposomes, in particular phospholipid liposomes, to reduce the risk of local side effects and to improve the acceptance by the user. Nevertheless, the preparations described in WO 2007/031519 comprise more than 70 wt.% of water and do not comprise any petroleum hydrocarbon.

DE 10 2010 044 785 describes cosmetic or dermatological preparations formulated as microemulsions comprising octenidine dihydrochloride as co-emulsier. Nevertheless, the preparations described in DE 10 2010 044 785 comprise more than 70 wt.% of water.

DE 10 2010 044 787 describe cosmetic or dermatological preparations formulated as macroemulsions comprising octenidine dihydrochloride as deodorant active ingredient. Nevertheless, the preparations described in DE 10 2010 044 787 comprise more than 70 wt.% of water and do not comprise any petroleum hydrocarbon.

However, none of these documents describe topical compositions comprising octenidine dihydrochloride which provide antiseptic properties and, at the same time, can provide additional benefits to the skin such as improving the skin barrier and increasing the skin moisture.

SUMMARY OF THE INVENTION

The present application refers to topical pharmaceutical or cosmetic compositions comprising:

(a) 0.01-3.0 wt.% of octenidine dihydrochloride;
(b) 1-20 wt.% of at least one petroleum hydrocarbon;
(c) 0.5-10 wt.% of at least one C_{6-24} fatty acid triglyceride;
(d) 1-20 wt.% of at least one C_{6-24} fatty alcohol;
(e) 1-15 wt% of at least one non-ionic surfactant;
(f) 1 to 20 wt% of at least one polyol; and
(g) 30-70 wt.% of water.
Said compositions are chemically stable, free of side effects and cosmetically acceptable. Therefore, said compositions are useful in the treatment of skin diseases or disorders selected from infected eczema (infected dermatitis or infected dermatoses), cutaneous bacterial infections or cutaneous fungal infections.

In addition, the composition of the invention can be used by patients suffering from atopic dermatitis and/or dry skin to prevent microbial proliferation and to restore the skin barrier function.

The invention further relates to the use of a composition as defined above for the manufacture of a medicament for the treatment or prevention of skin disorders or diseases selected from infected eczema (infected dermatitis), cutaneous bacterial infections or cutaneous fungal infections.

The invention further relates to the use of a composition as defined above to prevent microbial proliferation in patients suffering from atopic dermatitis and/or dry skin and to restore the skin barrier function.

The invention further relates to a method for treating a subject afflicted with skin disorders or diseases as defined above, which comprises applying to the affected area of skin of said subject an effective amount of a topical pharmaceutical composition as defined above.
DETAILED DESCRIPTION OF THE INVENTION

Octenidine dihydrochloride

Octenidine dihydrochloride \((N,N'-(1,10\text{-}\text{decanediyldi}-1\text{[4H]-pyridinyl}\text{-}4\text{-}yli}dene)\) \text{bis-(1-octanamine)}\) dihydrochloride; CAS RN 70775-75-6) is a bispyridine bactericidal antiseptic with some antiviral and antifungal activity having the empirical formula \(C_{36}H_{62}N_4\cdot2H_2O\), and a molecular weight of 623.8 g/mol (see Martindale - The complete drug reference, 32\textsuperscript{nd} edition, 1999, Disinfectants and Preservatives).

The topical pharmaceutical or cosmetic compositions

Typically, the present invention provides topical pharmaceutical or cosmetic compositions comprising:

(a) 0.01-3.0 wt.% of octenidine dihydrochloride;
(b) 1-20 wt.% of at least one petroleum hydrocarbon;
(c) 0.5-10 wt.% of at least one \(C_6-C_4\) fatty acid triglyceride;
(d) 1-20 wt.% of at least one \(C_6-C_{24}\) fatty alcohol;
(e) 1-15 wt% of at least one non-ionic surfactant;
(f) 1 to 20 wt% of at least one polyol; and
(g) 30-70 wt.% of water.

According to the invention, the term "topical composition" (or topical formulation) means any cosmetic product or preparation, which is applied or spread to the surface of the skin.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention the total amount of (a) octenidine dihydrochloride is in the range of 0.03-1.5 wt.%; more preferably 0.05-1.0 wt.%, based on the total weight of the composition.

Particularly preferred amounts of (a) octenidine dihydrochloride are 0.05 wt.%, 0.1 wt.% and 0.25 wt.%, based on the total weight of the composition.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (b) petroleum hydrocarbons is in the range of 3-15 wt.%, based on the total weight of the composition.
Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (c) C₆-C₄ fatty acid triglyceride is in the range of 1-5 wt.%, based on the total weight of the composition.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (d) C₆-C₄ fatty alcohol is in the range of 7-18 wt.%, based on the total weight of the composition.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (e) non-ionic surfactant is in the range of 2-10 wt.%, based on the total weight of the composition.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (f) polyol is in the range of 5-15 wt.%, based on the total weight of the composition.

Preferably, in the topical pharmaceutical or cosmetic compositions according to the invention, the total amount of (g) of water is in the range of 50-65 wt.%, based on the total weight of the composition.

Suitable petroleum hydrocarbons, i.e. mineral oils, paraffins and waxes from petroleum according to the present invention are: hard paraffin, liquid paraffin (Liquid Petrolatum or Paraffinum Liquidum), light liquid paraffin (Light Liquid Petrolatum or Paraffinum Perliquidum), white soft paraffin (White Petrolatum), yellow soft paraffin (Yellow Petrolatum), macrocrystalline paraffin waxes (which are mixtures which consist mainly of saturated C₁₈-C₉₀ hydrocarbons and smaller amounts of iso-alkanes and cycloalkanes with a molecular weight comprised between 250 and 450 g/mol and, although they are solids at room temperature, they have low melting points, usually comprised between 40°C and 60°C), microcrystalline paraffines waxes (which consist of C₄₀-C₅₅ compounds which contain, in addition to normal hydrocarbons, large amounts of iso-alkanes and naphtenes with long alkyl side-chains, the iso-alkanes forming microcrystals, the microcrystalline paraffines waxes having mean molecular weights comprised between 500 and 800 g/mol, being solids at room temperature, and having melting points comprised between 60°C and 90°C), or mixtures thereof.

Preferred petroleum hydrocarbons are hard paraffin, liquid paraffin, light liquid paraffin, white soft paraffin or mixture thereof, being particularly preferred liquid paraffin, white soft paraffin or mixtures thereof.
According to the present invention, the C<sub>6</sub>-C<sub>24</sub> fatty acid triglycerides are specifically triglycerin esters of linear and/or branched, saturated and/or unsaturated alkanecarboxylic acids with a chain length of 6 up to 24 carbon atoms, preferably of 8 up to 18 carbon atoms. The fatty acids esterifying the different positions of glycerin can be different, giving rise to a large amount of possible combinations, including positional combinations. The position of the different fatty acids in natural triglycerides is not random, but rather it depends on the origin of the fat. The triglycerides more simple are those constituted by a sole fatty acid.

Preferred C<sub>6</sub>-C<sub>24</sub> fatty acid triglycerides according to the present invention are chosen, for example, from the group consisting of synthetic, semi-synthetic and natural oils, as for example, animal fats and oils such as cow tallow, pig lard, bone oil, aquatic animal fats and oils (fish, such as herring, cod or sardine; cetaceans; etc.); and vegetable fats and oils such as avocado oil, almond oil, hazelnut oil, babassu palm oil, borage oil, peanut oil, canola oil, hemp oil, milk thistle oil, safflower oil, chufa oil, coconut oil, rapeseed oil, black cumin oil, wheat germ oil, sunflower oil, linseed oil, macadamia nut oil, corn oil, walnut oil, olive oil and its by-products such as olive pomace oil, palm oil and its fractions such as palm olein and palm stearin, evening primrose oil, rosehip oil, castor oil, rice bran oil, apricot kernel oil, cottonseed oil, pumpkinseed oil, palm kernel oil and its fractions such as palm kernel olein and palm kernel stearin, grape seed oil, sesame oil, soy oil, cocoa butter, shea butter and the like. C<sub>6</sub>-C<sub>24</sub> fatty acid triglycerides of the caproic, capric, caprylic, lauric, myristic, palmitic, palmitoleic, stearic, isostearic, 2-ethylhexanoic, oleic, ricinoleic, behenic type, or mixtures thereof are preferred, in particular, those from vegetable origin. Particular preferred C<sub>6</sub>-C<sub>24</sub> fatty acid triglycerides are of the caproic, capric, caprylic and lauric type, and mixtures thereof.

Suitable fatty alcohols according to the present invention are C<sub>6</sub>-C<sub>24</sub> fatty alcohols from vegetable and animal fats and oils such as those previously described, such as cotton, safflower, coconut, rapeseed, linseed, palm, palm kernel, sunflower, olein, olive, olive pomace, castor oil, tallow, soy, tall oil, etc, possibly totally or partially hydrogenated, as well as purified or synthetic fatty alcohols such as caproyl alcohol, capryl alcohol, capric alcohol, lauryl alcohol, myristyl alcohol, palmityl (cetyl) alcohol, palmitoyl alcohol, stearyl alcohol, isostearyl alcohol, 2-octyldecanol (isoarachidyl alcohol), 2-ethylhexanoyl alcohol, oleyl alcohol, ricinoleyl alcohol, elaidyl alcohol, petroselinic acid, linoleyl alcohol, linolenyl alcohol, arachidyl alcohol, gadoleyl alcohol, behenyl alcohol and erucyl alcohol, or technical grade mixtures thereof such as cetostearyl
alcohol. Fatty alcohols of the lauryl, myristyl, palmitoyl, stearyl, isostearyl, 2-octyldodecanol, 2-ethylhexanoyl, oleyl, ricinoleyl and behenyl type, or technical grade mixtures thereof as such as cetostearyl alcohol are preferred, in particular, those from vegetable origin.

Suitable non-ionic surfactants according to the present invention are acetoglycerides; diacetylated monoglycerides; mono- and di-acetylated monoglycerides; mono- and di-glycerides (such as glycercyl monobehenate, glycercyl dibehenate, glycercyl monooleate, glycercyl dioleate, glycercyl monostearate, glycercyl distearate, glycercyl mono- and di-palmitostearate or glycercyl dipalmitostearate); esters of ethylene glycol or propylene glycol with C₆-C₂₂ fatty acids (such as ethylene glycol monopalmitostearate, ethylene glycol monteostearate, propylene glycol monocaprylate, propylene glycol dicaprylate, propylene glycol dicaprylocaprate, propylene glycol monopalmistearate, propylene glycol monostearate or propylene glycol alginate); polyoxyethylene alkyl ethers [polyoxyethylene glycol ethers of n-alcohols such as lauryl, oleyl, myristyl, cetyl, and stearyl alcohol; such as macrogol cetostearyl ethers (polyoxyl 6 cetostearyl ether, polyoxyl 20 cetostearyl ether or polyoxyl 25 cetostearyl ether), macrogol cetearyl ethers (such as, polyoxyl 2 cetearyl ether, polyoxyl 10 cetearyl ether or polyoxyl 20 cetearyl ether), macroalgol lauryl ethers (such as polyoxyl 2 lauryl ether, polyoxyl 4 lauryl ether, polyoxyl 9 lauryl ether or polyoxyl 23 lauryl ether), macroalgol stearyl ethers (such as polyoxyl 2 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 21 stearyl ether or polyoxyl 100 stearyl ether), or macroalgol oleyl ethers (such as polyoxyl 2 oleyl ether, polyoxyl 10 oleyl ether or polyoxyl 20 oleyl ether)]; macroalgol monomethyl ethers (polyethylene glycol monomethyl ethers having nominal average molecular weight in the range of 300 to 10,000, preferably 320 to 4,000, more preferably in the range of 350 to 1,000, such as polyoxyethylene glycol 1000 monomethyl ether); menfegol; nonoxinols (such as nonoxinol 9, nonoxinol 10 or nonoxinol 11); octoxinols (such as octoxinol 9); poloxamers (copolymers of polyoxyethylene and polyoxypropylene, such as poloxamer 188 or poloxamer 188); polyoxyethylene castor oils (such as polyoxyl 35 castor oil); polyoxyethylene hydrogenated castor oil (such as polyoxyl 40 hydrogenated castor oil); polyoxyethylene stearates (polyethoxylated derivatives of stearic acid such as polyoxyl 2 stearate, polyoxyl 4 stearate, polyoxyl 6 stearate, polyoxyl 8 stearate, polyoxyl 12 stearate, polyoxyl 20 stearate, polyoxyl 40 stearate, polyoxyl 50 stearate, polyoxyl 100 stearate, polyoxyl 150 stearate, polyoxyl 4 distearate, polyoxyl 8 distearate, polyoxyl 12 distearate, polyoxyl 32 distearate or polyoxyl 150 distearate); polyoxyethylene sorbitan fatty acid esters (such as polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80 or polysorbate 85); propylene glycol diacetate (PGDA, which is the
reaction product of propylene oxide and acetic acid); sorbitan esters (such as sorbitan monolaurate, sorbitan mono-oleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate or sorbitan tristearate) and sucrose esters.

Preferred non-ionic surfactants according to the present invention are mono- and di-glycerides (such as glyceryl monobehenate, glyceryl dibehenate, glyceryl monooleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitostearate or glyceryl dipalmitostearate); esters of ethylene glycol or propylene glycol with C₆-C₁₂ fatty acids (such as ethylene glycol monopalmitostearate, ethylene glycol monostearate, propylene glycol monocaprylate, propylene glycol dicaprylate, propylene glycol dicaprylocaprate, propylene glycol monopalmitostearate, propylene glycol monostearate or propylene glycol alginate); polyoxyethylene alkyl ethers [polyoxyethylene glycol ethers of n-alcohols such as lauryl, oleyl, myristyl, cetyl, and stearyl alcohol; such as macrogol cetostearyl ethers (polyoxy 6 cetostearyl ether, polyoxy 20 cetostearyl ether or polyoxy 25 cetostearyl ether), macrogol cetearyl ethers (such as, polyoxy 2 cetyl ether, polyoxy 10 cetyl ether or polyoxy 20 cetyl ether), macrogol lauryl ethers (such as polyoxy 2 laurylether, polyoxy 4 laurylether, polyoxy 9 laurylether or polyoxy 23 laurylether), macrogol stearyl ethers (such as polyoxy 2 stearyl ether, polyoxy 10 stearyl ether, polyoxy 21 stearyl ether or polyoxy 100 stearyl ether), or macrogol oleyl ethers (such as polyoxy 2 oleyl ether, polyoxy 10 oleyl ether or polyoxy 20 oleyl ether)]; polyoxyethylene sorbitan fatty acid esters (such as polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80 or polysorbate 85); propylene glycol diacetate (PGDA, which is the reaction product of propylene oxide and acetic acid); and sorbitan esters (such as sorbitan monolaurate, sorbitan mono-oleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate or sorbitan tristearate).

Particularly preferred non-ionic surfactants according to the present invention are mono- and di-glycerides (such as glyceryl monobehenate, glyceryl dibehenate, glyceryl monooleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitostearate or glyceryl dipalmitostearate); esters of ethylene glycol or propylene glycol with C₆-C₁₂ fatty acids (such as ethylene glycol monopalmitostearate, ethylene glycol monostearate, propylene glycol monocaprylate, propylene glycol dicaprylate, propylene glycol dicaprylocaprate, propylene glycol monopalmitostearate, propylene glycol monostearate or propylene glycol alginate); and polyoxyethylene sorbitan fatty acid esters (such as polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80 or polysorbate 85).
Suitable polyols according to the present invention are preferably water-soluble polyols such as polyhydric alcohols with two or more hydroxyl groups in their molecule. Specific examples can include ethylene glycol, propylene glycol, 1,3- butylene glycol, 1,4-butylen glycol, hexylene glycol, dipropylene glycol, polyethylene glycol with average molecular weights by weight ranging between 100 and 1000, glucose, fructose, galactose, mannose, ribose, erythrose, maltose, maltitose, maltotriose, sucrose, xylitol, sorbitol, threitol, erythritol, glycerol, polyglycerol and starch alcohols. Preferred polyols according to the present invention are ethylene glycol, propylene glycol, 1,3-butylen glycol, 1,4-butylen glycol, hexylene glycol, dipropylene glycol, polyethylene glycol with average molecular weights by weight ranging between 100 and 1000, glycerol, polyglycerol, and mixtures thereof. Particularly preferred polyols according to the present invention are 1,3-butylen glycol, 1,4-butylen glycol, hexylene glycol, dipropylene glycol, glycerol, and mixtures thereof.

In a particularly preferred embodiment, the topical pharmaceutical or cosmetic compositions of the invention comprise, based on the total weight of the composition:
(a) 0.03-1.5 wt.% of octenidine dihydrochloride;
(b) 3-15 wt.% of at least one petroleum hydrocarbon;
(c) 1-5 wt.% of at least one C₆-C₄ fatty acid triglyceride;
(d) 7-18 wt.% of at least one C₆-C₄ fatty alcohol;
(e) 2-10 wt.% of at least one non-ionic surfactant;
(f) 5-15 wt.% of at least one polyol; and
(g) 50-65 wt.% of water.

In another particularly preferred embodiment, the topical pharmaceutical or cosmetic compositions of the invention comprise, based on the total weight of the composition:
(a) 0.01-3.0 wt.%, preferably 0.03-1.5 wt.% of octenidine dihydrochloride;
(b) 1-20 wt.% preferably 3-15 wt.% of at least one petroleum hydrocarbon selected from hard paraffin, liquid paraffin, light liquid paraffin, white soft paraffin and mixtures thereof;
(c) 0.5-10 wt.%, preferably 1-5 wt.% of at least one C₆-C₄ fatty acid triglyceride;
(d) 1-20 wt.% preferably 7-18 wt.% of at least one C₆-C₂₄ fatty alcohol;
(e) 1-15 wt.%, preferably 2-10 wt.% of at least one non-ionic surfactant selected from mono- and di-glycerides, esters of ethylene glycol or propylene glycol with C₆-C₂₂ fatty acids, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, propylene glycol diacetate, sorbitan esters, and mixtures thereof;
(f) 1 to 20 wt%, preferably 5-15 wt.% of at least one polyol selected from ethylene glycol, propylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, hexylene glycol, dipropylene glycol, polyethylene glycol with average molecular weights by weight ranging between 100 and 1000, glycerol, polyglycerol and mixtures thereof; and

(g) 30-70 wt.%, preferably 50-65 wt. % of water.

The topical pharmaceutical or cosmetic compositions according to the invention may optionally further comprise other well-known pharmaceutically and/or cosmetically acceptable additives, such as, e.g. anti-irritants agents, antioxidants agents, buffering agents (pH adjusting agents), chelating agents, emollients, natural waxes, penetration enhancing agents, preservative agents, silicones, solubilizing agents, thickening agents, wetting agents or mixtures thereof.

Examples of suitable anti-irritants are aloe vera, chamomile, alpha-bisabolol, cola nitida extract, green tea extract, tea tree oil, licorice extract, butyl alcohol (octadecyl glyceryl ether), selachyl alcohol (α-9-octadecenyl glyceryl ether), chimyl alcohol (ohexadecyl glyceryl ether), panthenol, allantoin, caffeine or other xanthines, glycyrrhizic acid and derivatives thereof, and mixtures thereof.

Antioxidants used can be any antioxidants which are suitable or customary for cosmetic and/or dermatological applications. Suitable antioxidants are advantageously selected from the group consisting of amino acids (for example glycine, histidine, tyrosine, tryptophan) and derivatives thereof, imidazoles (e.g. urocanic acid) and derivatives thereof, peptides such as D,L-carnosine, D-carnosine, L-carnosine and derivatives thereof (e.g. anserine), carotenoids, carotenes (e.g. a-carotene, β-carotene, lycopene) and derivatives thereof, lipoic acid and derivatives thereof (e.g. dihydrolipoic acid), aurothioglucose, propylthiouracil and other thiols (e.g. thioredoxin, glutathione, cysteine, cystine, cystamine and the glycosyl, N-acetyl, methyl, ethyl, propyl, amyl, butyl and lauryl, palmitoyl, oleyl, γ-linoleyl, cholesteryl and glyceryl esters thereof) and salts thereof, dilauryl thiodipropionate, distearil thiodipropionate, thiodipropionic acid and derivatives thereof (esters, ethers, peptides, lipids, nucleotides, nucleosides and salts) and sulphoximine compounds (e.g. bithionine sulphoximines, homocysteine sulphoximine, bithionine sulphones, penta-, hexa-, heptathionine sulphoximine) in very small tolerated doses (e.g. pmol to nM/kg), also (metal) chelating agents (e.g. o hydroxy fatty acids, palmitic acid, phytic acid, lactoferrin), a-hydroxy acids (e.g. citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and derivatives thereof, unsaturated fatty acids and derivatives thereof.
(e.g. γ-linolenic acid, linoleic acid, oleic acid), folic acid and derivatives thereof, ubiquinone and ubiquinol and derivatives thereof, vitamin C and derivatives (e.g. ascorbyl palmitate, Mg ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (e.g. vitamin E acetate), and coniferylbenzoate of benzoin, rutinic acid and derivatives thereof, ferulic acid and derivatives thereof, butylated hydroxytoluene, butylated hydroxyanisole, nordihydroguaiiac resin acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and derivatives thereof, mannose and derivatives thereof, zinc and derivatives thereof (e.g. ZnO, ZnSO₄), selenium and derivatives thereof (e.g. selenium methionine), stilbenes and derivatives thereof (e.g. stilbene oxide, trans-stilbene oxide) and the derivatives (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids) of said active ingredients which are suitable according to the invention.

Any pharmaceutically acceptable buffering agents to adjust the pH of the aqueous liquid pharmaceutical compositions according to the invention to be within the acceptable range for topical administration, preferably in the range of 3.0 to 6.0, more preferably in the range of 3.5 to 5, can be used. For example the inclusion in the composition of a pharmaceutically acceptable acid such as acetic, citric, fumaric, phosphoric, hydrochloric, lactic or nitric acids or the like, or a mixture thereof. It will also be understood that certain compositions of the invention can have a pH in the desired range without inclusion of a pH adjusting agent specifically for that purpose. Typically, however, an acidic buffer system is present in the composition to achieve the desired pH. An acidic buffer system comprises an acidulant and a buffering agent. Suitable acidulants will be known to those of skill in the art and illustratively include acetic, citric, fumaric, hydrochloric, phosphoric, lactic and nitric acids and the like, and mixtures thereof. Suitable buffering agents will likewise be known to those of skill in the art and illustratively include potassium metaphosphate, potassium phosphate, sodium phosphate, sodium acetate, sodium citrate, and the like, and mixtures thereof. Other buffer systems which are also suitable according to the invention are gluconic acid and sodium gluconate, glucono-delta-lactone (GDL) and sodium gluconate, mannoic acid and sodium mannoate, 3-deoxy-d-manno-2-ketose and sodium mannoate, L-gulonic acid and sodium L-gulonate, L-idonic acid and sodium L-idonate, or mixtures thereof.

Suitable emollients, which can be used in the composition of the present invention include, for example, dodecane, squalane, cholesterol, isohexadecane, isononyl isononanoate, PPG Ethers, petrolatum, lanolin, safflower oil, castor oil, coconut oil,
cottonseed oil, palm kernel oil, palm oil, peanut oil, soybean oil, polyol carboxylic acid esters, derivatives thereof, and the like, and combinations thereof.

Suitable natural waxes according to the present invention are the candelilla wax, carnauba wax, Japan wax, esparto wax, cork wax, guaruma wax, rice wax, sugar cane wax, ouricury wax, montan wax, beeswax, shellac wax, espermaceti, wool lanolin (wax), uropygial fat wax, ceresin waxes, peat waxes, ozokerite, as well as chemically modified waxes (hard waxes) for example, montan wax esters, waxes obtained by the Fischer-Tropsch process, hydrogenated jojoba waxes and synthetic waxes.

Examples of suitable penetration enhancing agents can include, e.g., dimethylsulfoxide (DMSO), N-methyl pyrrolidine, dimethyl formamide (DMF), allantoin, urazole, N,N-dimethylacetamide (DMA), decylmethylsulfoxide, polyethylene glycol monolaurate, propylene glycol, propylene glycol monolaurate, glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one, alcohols, glycerin, hyaluronic acid, transcutol, and the like, and combinations thereof. Certain oil components (e.g., certain vegetable oils such as, e.g., safflower oil, cottonseed oil and corn oil) also can exhibit penetration enhancing properties.

Examples of suitable preservatives to prevent microbial contamination are alkylparabens, particularly methylparaben, propylparaben and butylparaben; benzalkonium chloride; benzethonium chloride; benzoic acid; benzyl alcohol; sodium benzoate; bronopol; butylated hydroxy toluene; butylated hydroxyanisole; cetrimide; chlorobutanol; chlorocresol; chlorhexidine; dehydroacetic acid; ethylenediamine tetraacetic acid; paraben esters; phenylethylalcohol; phenol; phenoxyethanol; sorbic acid; potassium sorbate; and mixtures thereof. The amount of preservative generally utilized will vary depending upon the preservative selected.

Silicones suitable according to the present invention are cyclic and/or linear silicones, which can be found as monomers generally characterized by structural elements such as:

\[
\begin{align*}
R_1 \quad & \quad R_2 - \text{Si} - 0 - \\
& \quad \quad R_4
\end{align*}
\]

where the silicon atoms can be substituted by alkyl or aryl radicals equal or different, represented here generally by \(R_1\)-\(R_4\) groups.
Linear silicones with siloxane units suitable according to the present invention are generally characterized by structural elements such as:

\[
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{O-Si-} \quad \text{O-Si-} \\
\text{R}_3 \quad \text{R}_4
\end{array}
\]

where the silicon atoms can be substituted by alkyl or aryl radicals equal or different, are represented here generally by \( \text{R}_1-\text{R}_4 \) groups (meaning the number of different radicals is not necessarily limited to 4), \( m \) can take values from 2 to 200,000.

Cyclic silicones suitable according to the present invention are generally characterized by structural elements such as:

\[
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{O-Si-} \quad \text{O-Si-} \\
\text{R}_3 \quad \text{R}_4
\end{array}
\]

where the silicon atoms can be substituted by alkyl or aryl radicals equal or different, represented here generally by \( \text{R}_1-\text{R}_4 \) groups (meaning the number of different radicals is not necessarily limited to 4), \( n \) can take values from 3/2 to 20. Fractional values of \( n \) indicate that it may be odd numbers of siloxane groups present in the ring.

Specific examples include a cyclic methyl siloxane having the formula \([(\text{CH}_3)_2\text{SiO}]_x\) in which \( x \) is 3-6, or short chain linear methyl siloxanes having the formula \([(\text{CH}_3)_2\text{SiO}]_{\text{y}}\text{Si(CH}_3)_3\) in which \( y \) is 0-5.

Some suitable cyclic methyl siloxanes are hexamethyldicyclosiloxanes (D3), a solid with a boiling point of 134°C and the formula \([(\text{Me}_2\text{SiO})_3]_2\); octamethylcyclotetrasiloxane (D4) with a boiling point of 176°C, a viscosity of 2.3 mm²/s, and the formula \([(\text{Me}_2\text{SiO})_4]_2\); decamethylcyclopentasiloxane (D5) (cyclomethicone) with a boiling point of 210°C, a viscosity of 3.87 mm²/s, and the formula \([(\text{Me}_2\text{SiO})_5]_2\); and dodecamethylcyclohexasiloxane (D6) with a boiling point of 245°C, a viscosity of 6.62
mm²/s and the formula \((\text{Me}_2\text{SiO})_6\).

Some suitable short linear methyl siloxane are hexamethyldisiloxane (MM) with a boiling point of 100°C, viscosity of 0-65 mm²/s, and formula \(\text{Me}_3\text{SiOMe}_3\); octamethyltrisiloxane (MDM) with a boiling point of 152°C, viscosity of 1.04 mm²/s, and formula \(\text{Me}_3\text{SiMe}_2\text{SiOSiMe}_3\); decamethyltetrasiloxane (MD2M) with a boiling point of 194°C, viscosity of 1.53 mm²/s, and formula \(\text{Me}_3\text{SiO(MeSiO)}_2\text{SiMe}_3\); dodecamethylpentasiloxane (MD3M) with a boiling point of 229°C, viscosity of 2.06 mm²/s, and formula \(\text{Me}_3\text{SiO(Me}_2\text{SiO})_3\text{SiMe}_3\); tetradecamethylhexasiloxane (MD4M) with a boiling point of 245°C, viscosity of 2.63 mm²/s, and formula \(\text{Me}_3\text{SiO(Me}_2\text{SiO})_4\text{SiMe}_3\); and hexadecamethylheptasiloxane (MD5M) with a boiling point of 270°C, viscosity of 3.24 mm²/s, and formula \(\text{Me}_3\text{SiO(Me}_2\text{SiO})_5\text{SiMe}_3\).

Furthermore, long chain linear siloxanes such as phenyltrimethicone, bis(phenylpropyl)dimethicone, dimethicone, dimethiconol, cyclomethicone (octamethylcyclotetrasiloxane), hexamethylcyclotrisiloxane, poly(dimethylsiloxane), cetyldimethicone and behenoxy dimethicone are also included.

In addition, mixtures of cyclomethicone and isotridecyl isononanoate and of cyclomethicone and 2-ethylhexyl isostearate are also suitable silicones according to the invention.

Examples of solubilizing agents are, for example, nonionic surfactants from at least one of the following groups: products of the addition of 1 to 30 moles of ethylene oxide and/or 0 to 5 moles of propylene oxide onto linear \(\text{C}_6\text{C}_{22}\) fatty alcohols, \(\text{C}_{12}\text{C}_{22}\) fatty acids and alkyl phenols containing 8 to 15 carbons in the alkyl group; alkyl and/or alkenyl oligoglycosides containing 8 to 22 carbons in the alkyl group and ethoxylated analogs thereof; addition products of 1 to 15 moles of ethylene oxide with castor oil and/or hydrogenated castor oil; addition products of 15 to 60 moles of ethylene oxide with castor oil and/or hydrogenated castor oil; partial esters of glycerol and/or sorbitan with unsaturated or saturated, linear or branched fatty acids containing 12 to 22 carbons and/or hydroxy carboxylic acids containing 3 to 18 carbon atoms and addition products thereof with 1 to 30 moles of ethylene oxide; mixtures of alkoxylated glycerides and alkoxylated glycerine, partial esters of polyglycerol (average degree of selfcondensation 2 to 8), polyethylene glycol (weight average molecular weight 400 to 5000), trimethylolpropane, pentaerythritol, sugar alcohols (for example sorbitol), alkyl glucosides (for example methyl glucoside, butyl glucoside, lauryl glucoside) and
polyglucosides (for example cellulose) with saturated and/or unsaturated, linear or branched fatty acids containing 12 to 22 carbons and/or hydroxycarboxylic acids containing 3 to 18 carbons and addition products thereof with 1 to 30 moles of ethylene oxide; mixed esters of pentaerythritol, fatty acids, citric acid and fatty alcohol and/or mixed esters of fatty acids containing 6 to 22 carbons, methyl glucose and polyols, preferably glycerol or polyglycerol; mono-, di- and trialkyl phosphates and mono-, di- and/or tri-PEG-alkyl phosphates and salts thereof; block copolymers, for example Polyethylene glycol-30 Dipolyhydroxystearate; polymer emulsifiers; polyalkylene glycols and alkyl glyceryl ethers. Particularly preferred solubilizing agents are products of the addition of 1 to 30 moles of ethylene oxide and/or 0 to 5 moles of propylene oxide onto linear C₈-C₁₂ fatty alcohols such as lauryl, myristyl, cetyl (palmityl), stearyl, oleyl, and ricinoleyl alcohols, or technical grade mixtures thereof such as cetostearyl alcohol or palmitoleyl alcohol.

A thickening agent or viscosity-enhancing agent can be included to generally thicken the liquid pharmaceutical compositions. While any suitable thickening agent can be included in the compositions of the present invention, a preferred thickening agent, when used, includes one or more of acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, glycerin, gelatin guar gum, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum, and any combination thereof. More preferred thickening agents are glycerin, hydroxypropylmethylcellulose, and xanthan gum, and any combination thereof.

Examples of wetting agents (chemical substances that increase the spreading and penetrating properties of a liquid by lowering its surface tension) include one or more cationic surfactants, such as benzalkonium chloride; non-ionic surfactants such as polyethylene and polyoxypropylene block copolymers; polyoxyethylene fatty acid glycerides and oils (such as polyoxyethylene (6) caprylic/capric mono- and diglycerides), polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene sorbitan esters, such as polysorbate 20 and polysorbate 80; propylene glycol fatty acid esters, such as propylene glycol laureate; glyceryl fatty acid esters, such as glyceryl monostearate; sorbitan esters, such as sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; glyceryl fatty acid esters, for example glyceryl monostearate; anionic surfactants such as sodium lauryl sulphate,
sodium lauryl ether sulphate; or fatty acids and salts thereof, such as oleic acid, sodium oleate and triethanolamine oleate.

The pH value of the topical pharmaceutical or cosmetic compositions according to the invention is typically within the acceptable range for topical administration, and is preferably in the range of 3.0 to 9.0, more preferably in the range of 3.5 to 6.0.

Typically, the topical pharmaceutical or cosmetic compositions according to the invention is formulated in the form of a cream, a gel, an ointment, a paste, a suspension, a lotion, a foam, a spray, an aerosol or a solution.

In a particularly embodiment, the topical compositions according to the invention are cosmetic compositions, i.e. are classified in accordance with Regulation (EC) 1223/2009 (Regulation (EC) no 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products).

A "cosmetic composition" is considered as any substance or composition intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.

The viscosity of the topical pharmaceutical or cosmetic compositions according to the invention will depend on the form of the composition. For instance, in the case of a cream, the viscosity is typically in the range of 2,000 to 15,000 mPa.s, preferably in the range of 2,500 to 10,000 mPa.s, more preferably in the range of 3,000 to 7,000 mPa.s measured at 20°C using a DIN-Rotations Rheometer (Paar Physica); Measuring System Z 3 DIN ; D= 57 1/s.

In the case of a gel, the viscosity is typically in the range of 300 to 1,500 mPa.s, preferably in the range of 500 to 1,200 mPa.s, more preferably in the range of 600 to 900 mPa.s measured at 20°C using a DIN-Rotations Rheometer (Paar Physica); Measuring System Z 3 DIN ; D= 57.2/s.

In a preferred embodiment, the topical pharmaceutical composition according to the invention is formulated in the form of a cream.
As used herein, cream is a homogeneous, semi-solid preparation consisting of opaque emulsion systems. The consistency and rheological properties depend on the type of emulsion, either water-in-oil (w/o) or oil-in-water (o/w), and on the nature of the solids in the internal phase (International Pharmacopoeia, 4th edition).

The invention further relates to a topical pharmaceutical or cosmetic composition as defined above for use in the treatment or prevention of skin disorders or diseases selected from infected eczema (infected dermatitis), cutaneous bacterial infections or cutaneous fungal infections.

Typically, eczemas (dermatitis) are generally classified in the following types:

1. Contact dermatitis:
   1.1. Housewives hand eczema;
   1.2. Keratodermia tyloides palmaris progressiva;
   1.3. Diaper dermatitis;

2. Atopic dermatitis:
   2.1. Infantile atopic dermatitis;
   2.2. Childhood atopic dermatitis; and
   2.3. Adolescent and adult atopic dermatitis;

3. Seborrheic dermatitis;
4. Nummular eczema;
5. Lichen simplex chronicus (or lichen Vidal);
6. Autosensitization dermatitis;
7. Stasis dermatitis; and

8. Other eczemas:
   8.1. Pompholyx, dyshidrotic eczema;
   8.2. Pityriasis simplex faciei; and
   8.3. Perioral dermatitis.

In a preferred embodiment, the infected eczema according to the invention is selected from infected contact dermatitis, infected atopic dermatitis, infected seborrheic dermatitis, infected nummular eczema, infected lichen simplex chronicus, infected autosensitization dermatitis and infected stasis dermatitis. Preferably, the infected eczema according to the invention is selected from infected contact dermatitis, infected atopic dermatitis, infected seborrheic dermatitis, being infected atopic dermatitis particularly preferred.
Typically, the infection is caused by *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus pyogenes*, *Serratia marcescens* or *Pseudomonas aeruginosa*.

Cutaneous bacterial infections are caused by resident or transient bacteria in the epidermis and mucosa. Typically, cutaneous bacterial infections are classified by the clinical features in four main subtypes:

1. Acute cutaneous infections (acute pyoderma);
2. Chronic cutaneous infections (chronic pyoderma);
3. Systemic infections caused by toxins that are produced by bacteria; and
4. Diseases with specific clinical features that are caused by specific bacteria.

In a preferred embodiment, the cutaneous bacterial infections according to the invention are selected from Impetigo (impetigo contagiosa), Erysipelas, cellulitis, folliculitis (acne vulgaris), Hidradenitis suppurativa, Dermatitis papillaris capillitii, Pyodermia chronica glutealis, Trichomycosis palmellina, and Erythrasma.

Cutaneous fungal infections are caused by fungi, which are eukaryotic microorganisms that have a cellular wall and do not photosynthesize. They parasitize organisms or exist as spores. In superficial mycoses, fungi invade keratinized tissue such as the horny cell layer, hair and nails. In deep fungal infection, fungi tend to parasitize the dermis and deeper layers. Typically, cutaneous fungal infections are classified in:

1. Dermatophytoses;
2. Candidiases;
3. Malassezia infections; and
4. Other deep fungal infections.

In a preferred embodiment, the cutaneous fungal infections according to the invention are selected from Tinea pedis, Tinea unguium, Tinea manuum, Tinea cruris, Tinea corporis, Tinea faciei, Tinea capitis, Tinea incognito, Kerion (celsi), Tinea barbae, Candida intertrigo (Candida albicans), Interdigital candidiasis, Periungual candidiasis, Candida onychomycosis, Vulvovaginal candidiasis, Chronic mucocutaneous candidiasis, Pityriasis versicolor (Tinea versicolor), Pityrosporum folliculitis, Sporotrichosis, Chromoblastomycosis (Chromomycosis), Cutaneous cryptococcosis, Cutaneous aspergillosis, Cutaneous zygomycosis (mucormycosis), and Protothecosis cutanea.
The invention further relates to the use of a topical pharmaceutical or cosmetic composition as defined above for the manufacture of a medicament for the treatment or prevention of skin disorders or diseases selected from infected eczema (infected dermatitis or infected dermatoses), cutaneous bacterial infections or cutaneous fungal infections.

The invention further relates to the use of a composition as defined above for the manufacture of a medicament for the treatment or prevention of skin disorders or diseases selected from infected eczema (infected dermatitis), cutaneous bacterial infections or cutaneous fungal infections.

The invention further relates to the use of a composition as defined above to prevent microbial proliferation in patients suffering from atopic dermatitis and/or dry skin and to restore the skin barrier function.

The invention further relates to a method for treating a subject afflicted with skin disorders or diseases as defined above, which comprises applying to the affected area of skin of said subject an effective amount of a topical pharmaceutical or cosmetic composition as defined above.

The method of using the topical pharmaceutical composition of the invention is by applying it to completely cover the affected area, forming an occlusive barrier. The usual frequency of application is once or twice daily, preferably twice daily. The amount needed depends upon the size of the lesion site.

Typically, the area of the skin affected by the disease or disorder is selected from the group consisting of the face, ears, scalp, neck, forearms, back, legs, arms and hands.

The following examples are given in order to provide a person skilled in the art with a sufficiently clear and complete explanation of the present invention, but should not be considered as limiting of the essential aspects of its subject, as set out in the preceding portions of this description.
EXAMPLES

Example 1
1.1. A composition according to the invention was prepared as indicated in Table 1 (wt.% based on the total weight of the composition)

Table 1 - Octenidine dihydrochloride cream 0.1 wt.%

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>wt.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octenidine dihydrochloride</td>
<td>0.1</td>
</tr>
<tr>
<td>Cetostearyl alcohol</td>
<td>9.0</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td>2.0</td>
</tr>
<tr>
<td>Caprylic / Capric Triglyceride</td>
<td>2.0</td>
</tr>
<tr>
<td>Mineral Oil</td>
<td>3.0</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>5.0</td>
</tr>
<tr>
<td>Glyceryl Monostearate</td>
<td>2.0</td>
</tr>
<tr>
<td>Propylene Glycol Stearate</td>
<td>1.0</td>
</tr>
<tr>
<td>Octyldodecanol</td>
<td>5.0</td>
</tr>
<tr>
<td>Butylene glycol</td>
<td>8.0</td>
</tr>
<tr>
<td>Purified Water</td>
<td>up to 100 %</td>
</tr>
<tr>
<td>pH adjusted to 3.5-4.5</td>
<td></td>
</tr>
</tbody>
</table>

1.2. A composition according to the invention was prepared as indicated in Table 2 (wt.% based on the total weight of the composition)
The compositions described in Table 1 and Table 2 were prepared in the following manner:

1) Oil phase:
   The items Cetostearyl Alcohol, Polysorbate 40, Caprylic / Capric Triglyceride, Paraffin liquid, Paraffin white soft, Glyceryl Monostearate, Propylene Glycol Stearate and Octyldecanol are added to a stainless steel container. The ingredients are heated to 70°C and melted while stirring.

2) Water phase:
   Water and butylene glycol are mixed in a stainless steel container and heated to 70°C. The buffer substances are added and completely dissolved while stirring. The mixture is stirred for 30 minutes at 70°C.

3) Combination:
   The hot aqueous phase is transferred to the oil phase (stage 2) while homogenizing and stirring.

4) The emulsion is cooled down to 55°C while stirring. Octenidine hydrochloride is added while homogenizing and stirring.

5) The formulation is cooled down to room temperature while stirring.
Example 2
The efficacy of the composition of Example 1.2 in improving the skin barrier in subjects with a disturbed skin barrier was assessed with clinical control. 20 male or female subjects, aged 18 years old or older, with manifest atopic dermatitis used the cream of Example 1.2 during 2 weeks. The composition was applied twice a day (morning and evening) on one test area with a minimum area of 300 cm² (preferably on the limbs). Measurement of the physical skin parameters "transepidermal water loss" (TEWL) - as method for determining the integrity of the skin barrier function; and skin moisture by corneometry were performed on days 1 (baseline), 4, 8 and 15. In parallel, clinical assessment of dermal reactions (erythema and dryness) was performed by scoring.

2.1. Transepidermal water loss (TEWL)
TEWL was measured using a Tewameter (TM 300, Courage & Khazaka, either attached to an MPA9 central unit and a PC with the appropriate software or as a stand-alone device). Sensors (hygrosensors and thermistors) mounted in an 11 mm diameter open chamber in the probe measure the water pressure gradient above the skin. This allows quantification of diffusion of water through the skin, i.e. the TEWL. The probe was placed without pressure on one previously determined test field on the application area. Measurement was performed until a stable value for TEWL was reached. The mean baseline TEWL measured on Day 1 was 19.8 ± 8.0 g/m²h. Results of the TEWL are indicated in Table 1 expressed as mean % change from baseline (g/m²h)

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 4</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEWL measurements</td>
<td>-7%</td>
<td>-18%</td>
<td>-16%</td>
</tr>
</tbody>
</table>

2.2. Corneometry
The hydration of the stratum corneum was assessed by measuring the electrical capacitance of the skin using a Corneometer (CM 825, Courage & Khazaka) attached to an MPA5 central unit and a PC with the appropriate software. The principle of corneometric measurements is based on the large difference in the dielectric constant of water compared to other substances found in the stratum corneum.
While measuring, some of the water contained in the stratum corneum reaches the stray field of the probe capacitor, changing its capacitance. This capacitance is then processed to a digital measurement value that is proportional to the moisture content of the skin. The probe ahead is coated with a thin layer of glass. Thus, no ohmic contact between the measured object and the probe is present, preventing ionic conductance and polarization effects with could influence the measurement.

Three previously selected test fields on the application area were measured and the three measuring values (arbitrary units [a.u.]) were taken. The mean of the three corneometric values was used for the statistical analysis. The mean baseline corneometry value at Day 1 was 12.9 ± 7.6 a.u. Results of the corneometry measurements are indicated in Table 2 expressed as mean % change from baseline (a.u.)

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 4</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEWL measurements</td>
<td>28%</td>
<td>46%</td>
<td>56%</td>
</tr>
</tbody>
</table>

2.3. Erythema
At baseline (Day 1) mild erythema (score 1) was observed in 45% of the subjects and erythema was absent (score 0) in 55% of the subjects.

At the end of the 2-week treatment phase (Day 15) with the composition of Example 1.2 erythema was absent in most of the subjects (80%). Mild erythema (score 1) was noted in 20% of the subjects.

2.4. Dryness
Mild dryness (score 1) was observed in 55% of the subjects and moderate dryness (score 2) was observed in 45% of the subjects at Day 1.

At the end of the 2-week treatment phase (Day 15) with the composition of Example 1.2 dryness was absent in 45% of the subjects. Mild dryness was observed in 20% of the subjects and moderate dryness was observed in 35% of the subjects.

The twice daily application the composition of Example 1.2 over two weeks revealed a positive effect on the skin barrier function. This was confirmed by TEWL and
corneometric measurements as well as by clinical assessment (erythema and dryness).

From the experimental results it can be concluded that the compositions of the invention are safe, cosmetically acceptable, and improve the skin condition (skin barrier was improved and skin moisture was increased) after repeated application.

Modifications, which do not affect, alter, change or modify the essential aspects of the compounds, combinations or pharmaceutical compositions described, are included within the scope of the present invention.
CLAIMS

1. A topical pharmaceutical or cosmetic composition comprising:
   (a) 0.01-3.0 wt.% of octenidine dihydrochloride;
   (b) 1-20 wt.% of at least one petroleum hydrocarbon;
   (c) 0.5-10 wt.% of at least one C₆-C₂₄ fatty acid triglyceride;
   (d) 1-20 wt.% of at least one C₆-C₂₄ fatty alcohol;
   (e) 1-15 wt% of at least one non-ionic surfactant;
   (f) 1 to 20 wt% of at least one polyol; and
   (g) 30-70 wt.% of water.

2. A composition according to claim 1, wherein the total amount of (a) octenidine dihydrochloride is in the range of 0.03-1.5 wt.%, more preferably 0.05-1.0 wt.%, based on the total weight of the composition.

3. A composition according to any one of the preceding claims, wherein the total amount of (b) petroleum hydrocarbon is in the range of 3-15 wt.%, based on the total weight of the composition.

4. A composition according to any one of the preceding claims, wherein the total amount of (c) C₆-C₂₄ fatty acid triglyceride is in the range of 1-5 wt.%, based on the total weight of the composition.

5. A composition according to any one of the preceding claims, wherein the total amount of (d) C₆-C₂₄ fatty alcohol is in the range of 7-18 wt.%, based on the total weight of the composition.

6. A composition according to any one of the preceding claims, wherein the total amount of (e) non-ionic surfactant is in the range of 2-10 wt.%, based on the total weight of the composition.

7. A composition according to any one of the preceding claims, wherein the total amount of (f) polyol is in the range of 5-15 wt.%, based on the total weight of the composition.
8. A composition according to any one of the preceding claims, wherein the total amount of (g) water is in the range of 50-65 wt.%, based on the total weight of the composition.

9. A composition according to any one of the preceding claims, comprising based on the total weight of the composition:
   (a) 0.03-1.5 wt.% of octenidine dihydrochloride;
   (b) 3-15 wt.% of at least one petroleum hydrocarbon;
   (c) 1-5 wt.% of at least one C₆-C₂₄ fatty acid triglyceride;
   (d) 7-18 wt.% of at least one C₆-C₂₄ fatty alcohol;
   (e) 2-10 wt.% of at least one non-ionic surfactant;
   (f) 5-15 wt.% of at least one polyol; and
   (g) 50-65 wt.% of water.

10. A composition according to claim 1, comprising based on the total weight of the composition:
   (a) 0.01-3.0 wt.% of octenidine dihydrochloride;
   (b) 1-20 wt.% of at least one petroleum hydrocarbon selected from hard paraffin, liquid paraffin, light liquid paraffin, white soft paraffin and mixtures thereof;
   (c) 0.5-10 wt.% of at least one C₆-C₂₄ fatty acid triglyceride;
   (d) 1-20 wt.% of at least one C₆-C₂₄ fatty alcohol;
   (e) 1-15 wt.% of at least one non-ionic surfactant selected from mono- and diglycerides, esters of ethylene glycol or propylene glycol with C₆-C₂₂ fatty acids, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, propylene glycol diacetate, sorbitan esters, and mixtures thereof;
   (f) 1 to 20 wt.% of at least one polyol selected from ethylene glycol, propylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, hexylene glycol, dipropylene glycol, polyethylene glycol with average molecular weights by weight ranging between 100 and 1000, glycerol, polyglycerol and mixtures thereof; and
   (g) 30-70 wt.% of water.

11. A composition according to any one of the preceding claims, wherein the composition further comprises anti-irritants agents, antioxidants agents, buffering agents, chelating agents, emollients, penetration enhancing agents, preservative agents, solubilizing agents, thickening agents, wetting agents or mixtures thereof.
12. A composition according to any one of the preceding claims, wherein the composition has a pH value in the range of 3.0 to 9.0.

13. A composition according to any one of the preceding claims, wherein the composition is formulated in the form of a cream, a gel, an ointment, a paste, a suspension, a lotion, a foam, a spray, an aerosol or a solution.

14. A composition as defined in any one of claims 1 to 13, for use in the treatment or prevention of skin disorders or diseases selected from infected eczema (infected dermatitis), cutaneous bacterial infections or cutaneous fungal infections.

15. Use of a composition as defined in any one of claims 1 to 13, for the manufacture of a medicament for the treatment or prevention of skin disorders or diseases as defined in claim 14.

16. Method for treating a subject afflicted with skin disorders or diseases as defined in claim 14, which comprises applying to the affected area of skin of said subject an effective amount of a composition as defined in any one of claims 1 to 13.
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/49 A61Q19/00 A61K9/00 A61K9/107 A61K31/4425
ADD.

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)
A61K A61Q

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 practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>wo 2007/031520 A2 (AI R LIQUE DESANTE INT) 22 March 2007 (2007-03-22) page 2, line 34 - page 3, line 26 page 6, line 18 - line 29 page 7, line 20 - line 26 examples 1,2 -----</td>
<td>1-16</td>
</tr>
<tr>
<td>Y</td>
<td>wo 2007/031519 A2 (AI R LIQUE DESANTE INT) [FR]: SCHUELKE &amp; MAYR GMBH [DE]: BEHREND SABINE 22 March 2007 (2007-03-22) page 2, line 37 - page 3, line 39 page 6, line 4 - page 7, line 31 example 2 -----</td>
<td>1-16</td>
</tr>
</tbody>
</table>

* Special categories of cited documents:

A: document defining the general state of the art which is not considered to be of particular relevance
E: earlier application or patent but published on or after the international filing date
L*: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O*: document referring to an oral disclosure, use, exhibition or other means
P*: document published prior to the international filing date but later than the priority date claimed
T*: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X*: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y*: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
A*: document member of the same patent family

Date of the actual completion of the international search
24 February 2015

Date of mailing of the international search report
06/03/2015

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016

Authorized officer
Girop, Annalisa
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>DE 10 2010 044787 A1 (BEIERSDORF AG [DE])</td>
<td>1-16</td>
</tr>
<tr>
<td></td>
<td>15 March 2012 (2012-03-15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0001]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0017]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0064]</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>DE 10 2010 044785 A1 (BEIERSDORF AG [DE])</td>
<td>1-16</td>
</tr>
<tr>
<td></td>
<td>15 March 2012 (2012-03-15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0001]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0022]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paragraph [0075]</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>EP 0 185 490 A2 (EURO CELTIQUE SA [LU])</td>
<td>1-16</td>
</tr>
<tr>
<td></td>
<td>column 3, line 1 - line 48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>examples</td>
<td></td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1928411 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5631932 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009507892 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2012229221 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008221165 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2007031520 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1926473 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2537514 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2451527 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009507891 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008254084 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2007031519 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2613758 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2012031984 A2</td>
</tr>
<tr>
<td>DE 102010044785 A1</td>
<td>15-03-2012</td>
<td>DE 112011103003 A5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2012031987 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 576278 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 5085985 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 1260833 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 85109101 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3584236 DL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 574185 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 8706437 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 854886 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR 852972 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IE 598278 B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 77224 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP H0699298 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP S61186312 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 854943 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 214496 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 81618 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4671957 A</td>
</tr>
</tbody>
</table>