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54. TITULO FORMULACIONES PARA EL CUIDADO DE LA PIEL HIPOALERGENICAS Y NO
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71. SOLICITANTE PATRICK FRANKE

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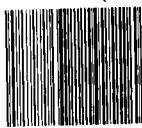
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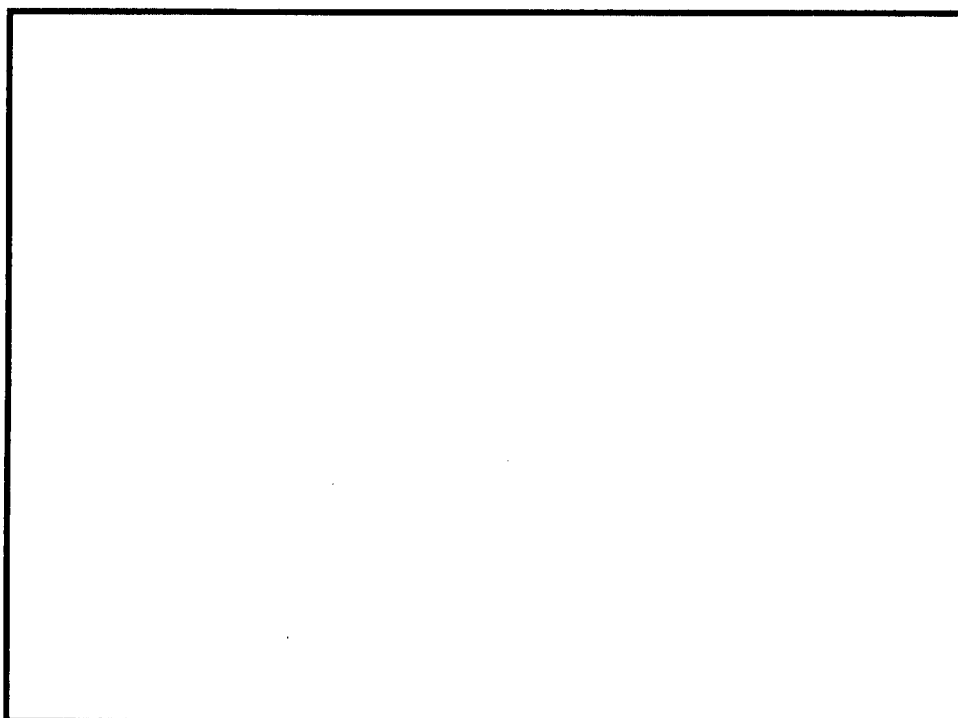
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros Tarjeta de propietarios.

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA: 

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

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***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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(54) Title: **HYPOALLERGENIC AND NON-IRRITANT SKIN CARE FORMULATIONS**

(57) Abstract: The invention provides novel hypoallergenic and non-irritant medical skin care formulations being water-in-oil emulsions. The formulations are free from ingredients with a known allergenic potential, such as fragrances, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins, thus being particularly suitable for patients with sensitive dry skin. The skin care formulations of the invention are useful in the prophylaxis and treatment of dry, sensitive skin or in the therapy or therapy support of eczematous or psoriatic skin and exhibit favorable sensorial properties. The invention furthermore provides a method of manufacturing the novel hypoallergenic and non-irritant skin care formulations.

WO 02/47642 A1

Hypoallergenic and non-irritant skin care formulations

Field of the Invention

This invention relates to hypoallergenic and non-irritant skin care formulations. The formulations of the invention are particularly suitable for medical applications such as for treating dry, sensitive skin and for therapy of skin conditions such as eczema and psoriasis. The formulations of the invention are compliance-friendly and superior to previously known formulations claiming to be hypoallergenic and non-irritant.

Background of the Invention

Human skin acts as a barrier and protective layer against chemical, physical and mechanical insults. The primary function of the skin's outer layer—the horny layer—is to prevent loss of water and vital substances into the environment while keeping noxious exogenous materials from penetrating to living tissue. The person skilled in the art refers to the outer horny layer as the *stratum corneum* (SC). Other functions of the SC include regulation of homeostatic mechanisms to assure steady-state conditions in the face of a changing environment, mechanisms of repair after disruption of the barrier by disease or exogenous insults and the presence of anti-bacterial substances to protect against infection. In order to fulfill these functions, the SC needs to be hydrated and flexible.

Complicated mechanisms in the skin maintain the essential hydration state of the SC. However, many factors work to compromise the SC barrier and increase the rate of water loss. Exposure to harsh conditions, including cold, dry winter weather, frequent washing with soap and hot water, exposure to surfactants or irritating chemicals or solvents may cause skin dryness. Apart from external factors provoking dry skin conditions, several diseases are known that are characterized by an abnormal condition or behavior of the SC. Examples of these diseases are atopic dermatitis, psoriasis and ichthyosis.

The SC sheds clusters of cells known as corneocytes from the surface of the skin while continuously replenishing them from underlying layers. This process is usually imperceptible due to the small size of the clusters, but in dry skin, the larger aggregates of

these cells are shed as scales or flakes. Dry skin is characterized by a rough, dry feeling and flaky appearance. It may itch and become red and irritated, and persons suffering from very dry skin (xerosis) may scratch affected areas repeatedly. If such conditions are untreated, severely dry skin may crack and bleed. Accumulation of thick brittle scales may occur such as in psoriasis and various forms of ichthyosis.

Skin moisturizers are used to help prevent skin from becoming dry or to return dry skin to its normal condition. Several compounds are known to act as skin moisturizers or humectants. Among these are glycerol (glycerin), urea, petrolatum (petroleum jelly), polyethylene glycols (PEGs), lanolins (wool wax), lactic acid (lactate), and ceramides. In skin care products, these ingredients are formulated together with a large variety of other ingredients used for maximizing efficacy, stability and shelf life. For skin care products, the subjective impressions of the user are particularly important. Thus, ingredients for improving subjective properties such as stickiness/greasiness, distribution/spreading, absorption, odor, or color are also added. Typically, skin care products are comprised of about 20–50 different ingredients, since it is the experience of the personal skilled in the art that favorable results may not be achieved by formulations with fewer ingredients.

The ingredients of skin care formulations are generally combined to form an emulsion, since they consist of hydrophobic and hydrophilic ingredients. In principle, two basic types of emulsions are possible. In an oil-in-water (O/W) emulsion, the oil phase forms the discontinuous phase, whereas in a water-in-oil (W/O) emulsion, the water phase represents the discontinuous phase.

Most skin care products are formulated as O/W emulsions. O/W emulsions are usually preferred for cosmetics, due to their favorable cosmetic properties that are pleasing for consumers. An O/W emulsion however represents a trade off in favor of such user-pleasing properties, since O/W-emulsions are generally less effective than W/O emulsions in treating or ameliorating dry skin conditions.

It has been suggested that W/O emulsions are suitable as an adjunctive therapy in the treatment of psoriasis, thus providing a steroid-sparing effect (Watsky et al., 1992, *Cutis*

50, 1992). In U.S. Patent No. 5,561,166, Sattler et al., a W/O composition containing urea and salts of lactic acid for the treatment of dry skin was disclosed. Additionally, U.S. Patent No. 5,552,147 discloses cosmetic compositions containing alpha hydroxy carboxylic acids dispersed in petroleum jelly with the aid of a phosphatide.

5

A common problem associated with skin care products is that they cause adverse effects in consumers or patients. Such unwanted effects include irritation (subjective and objective), allergic contact dermatitis, photocontact dermatitis, and immediate contact reactions ("*Dry Skin and Moisturizers: Chemistry & Function*", p. 403, Eds. Loden & Maibach, 2000). In this context, it should be understood that irritant reactions are distinct to allergenic reactions due to their different characteristics and/or mode of action. Established techniques such as patch testing are known to those skilled in the art and can be used to differentiate between the two types of reaction (see e.g., "*Unwanted effects of cosmetics and drugs used in dermatology*", pp. 6-10, Eds. de Groot, Weyland and Nater, Elsevier 1994).

15

The most frequently observed side effect is allergic contact dermatitis. This reaction is usually caused by fragrances and preservatives present in these products. Another origin of allergic reactions are moisturizers such as lanolin and its derivatives, emulsifiers such as cocamidopropyl betaine, and emollients.

20

Although many of the ingredients typically used in skin care formulations have a known irritation or allergenic sensitization potential and the rate of allergenic reactions in consumers or patients has increased dramatically over the last few years, these ingredients are still used in the majority of products in the skin care market of today. Several skin care formulations claim to be low in certain allergens and/or irritants. U.S. Patent No. 5,863,546 discloses cosmetic compositions, which differ significantly from the skin formulations of the invention, that exclude certain allergens and irritants.

25

The prior art has failed to provide a skin care formulation that avoids irritant and allergenic ingredients but retains favorable properties, in particular in the field of medical skin care. This may be attributed to the fact that strictly avoiding such ingredients undermines other

30

desired properties such as effective moisturizing of dry skin, stability of the formulation and favorable sensory attributes from the point of the view of the patient/consumer.

Accordingly, there is a need for a hypoallergenic and non-irritant skin care formulation that
5 effectively moisturizes dry, sensitive skin while at the same time exhibiting physical/microbiological stability and meeting the subjective aesthetic expectations of the patient/consumer.

10 Object and Summary of the Invention

It is an object of the present invention to solve the problems associated with available and known skin care formulations by providing a hypoallergenic and non-irritant skin care formulation. Aside from being hypoallergenic and non-irritant, the formulations of the invention effectively moisturize dry, sensitive skin and are stable and pleasing to the
15 patient/consumer. The formulations of the invention are suitable for medical skin care, such as for the therapy or therapy support of psoriasis and eczema.

The formulations of the invention are free from ingredients such as perfumes or perfume substitutes (fragrances), preservatives, colorings, plant extracts, polyethylene glycols
20 (PEGs), cetylstearyl alcohol, lanolin alcohols, lower alcohols, proteins and other substances with known allergenic potential, thus being particularly suitable for patients with sensitive skin. However, it is noted that the term "free from ingredients with known allergic potential" is intended to mean that such substances are not purposefully included in the formulations, although they might be present in very limited amounts, e.g. as a
25 contaminant of other ingredients. Since the allergenic and/or irritant potential of the ingredients is generally known to be dependent on their concentration, it should be understood that the presence of very limited amounts of such ingredients is still meant to be within the scope of the present invention.

30 The formulations of the invention comprise a water phase dispersed in an oil phase. In this embodiment, the oil phase may comprise cetearyl octanoate, dicaprylyl ether,

caprylic / capric triglyceride, polyglyceryl-3-diisostearate and polyglyceryl-2-dipolyhydroxystearate.

5 In one aspect of the invention, the formulations have relatively few ingredients, preferably less than 15, most preferably 12 or 13 ingredients.

In another aspect of the invention, the water phase of the formulations comprises the ingredients purified water, magnesium sulfate, lactic acid and sodium lactate. Additionally, the water phase may further comprise glycerin.

10

In one embodiment, the oil phase of the formulation may further comprise petrolatum and cera alba. Additionally, the oil phase may comprise ethylhexylglycerin or, alternatively, the water phase may further comprise propylene glycol.

15 In a second embodiment, the oil phase may further comprise ethylhexylglycerin. In this second embodiment, the water phase may further comprise urea.

20

The invention furthermore provides a method of manufacturing the hypoallergenic and non-irritant skin care formulations of the invention. It also provides formulations further comprising one or more pharmaceutically active compounds, vitamins or vitamin analogs, and/or a sunscreen, as well as formulations for use in the prophylaxis and treatment of dry, sensitive skin or in the therapy of eczematous or psoriatic skin.

25

It is another object of the invention to provide a method for the prophylaxis and treatment of dry, sensitive skin or for therapy support of eczematous skin and psoriatic skin by topically administering a therapeutically effective amount of the dermatological skin care formulations of the present invention.

30

Detailed Description of the Invention

The invention provides hypoallergenic and non-irritant skin care formulations having superior properties. The formulations of the invention, exemplary embodiments of which

are described in more detail below, are particularly suitable for medical skin care and for the treatment of dry, sensitive skin. Despite being free from such ingredients as perfumes or perfume substitutes, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins, the formulations of the invention
5 unexpectedly retain many desirable properties.

Although many of the ingredients commonly used in skin care formulations are not present, the skin care formulations of the invention are highly effective with maximal skin tolerance. For the formulations, the inventor chose raw materials with a proven skin
10 tolerance and a high physicochemical and microbiological stability. Focusing on the properties of the individual ingredients, the inventor selected a mixture of skin lipids on the basis of sensorial properties, tactility and polarity. Furthermore, in order to overcome the problems of the prior art, substances with known allergenic or irritant potential were eliminated and only selected ingredients, preferably possessing multifunctional properties,
15 and modern types of biodegradable emulsifiers are employed. These formulations exhibit a high degree of dispersity and are suitable for application in climate zone IV.

Though suitable for medical use, the skin care formulations of the invention have favorable cosmetic properties, such as excellent absorption, lack of stickiness, scent, and oily shine.
20 This is evidenced by the results of sensory assessment studies performed with several embodiments of the invention (see Table 3).

The formulations of the invention furthermore exhibit excellent physical/microbiological stability (see Example 4) and fulfill the requirements of the cosmetic directives of the
25 European Union and the United States. The formulations are physicochemically stable and meet the United States Pharmacopeia (USP) requirements in terms of microbiological stability. Although free of any preservatives, a shelf life of at least 2 years can be expected for the formulations of the invention.

30 In a preferred embodiment of the present invention, the skin care formulation is in the form of a semi-solid formulation (cream), which is particularly suitable for topical application to the face. Such a formulation is preferably a W/O emulsion.

The following table lists the ingredients of such a preferred formulation of the invention wherein each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

5

<u>(A) oil phase</u>		preferred	more preferred	most preferred
petrolatum	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
cetearyl octanoate	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
cera alba	0.5 – 4 %	1.0 – 2.5 %	1.5 – 2.5 %	1.75 – 2.25 %
polyglyceryl-3-diisostearate	3 – 6 %	4 – 5 %	4.25 – 4.75 %	4.4 – 4.6 %
polyglyceryl-2-dipolyhydroxystearate	0.5 – 3 %	1 – 2 %	1.25 – 1.75 %	1.4 – 1.6 %
ethylhexylglycerin	0 – 1 %	0 – 0.8 %	0.2 – 0.6 %	0.25 – 0.5 %
<u>(B) water phase</u>				
glycerin	0 – 7 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.2 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	0.05 – 0.5 %	0.05 – 0.25 %
sodium lactate	0.5 – 6 %	1 – 5 %	1.5 – 2.5 %	1.6 – 2.0 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

In a second preferred embodiment, the semi-solid (cream) formulation comprises the following ingredients, wherein each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

10

<u>(A) oil phase</u>		preferred	more preferred	most preferred
petrolatum	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
cetearyl octanoate	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
cera alba	0.5 – 4 %	1.0 – 2.5 %	1.5 – 2.5 %	1.75 – 2.25 %
polyglyceryl-3-diisostearate	3 – 6 %	4 – 5 %	4.25 – 4.75 %	4.4 – 4.6 %
polyglyceryl-2-dipolyhydroxystearate	0.5 – 3 %	1 – 2 %	1.25 – 1.75 %	1.4 – 1.6 %
<u>(B) water phase</u>				
glycerin	0 – 7 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.2 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	0.05 – 0.5 %	0.05 – 0.25 %
sodium lactate	0.5 – 6 %	1 – 5 %	1 – 3 %	1 – 2.5 %
propylene glycol	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

Preferably, the above formulation is a W/O emulsion. It is also particularly suitable for application to the face.

In a third preferred embodiment of the invention, the skin care formulation is in the form of a semi-liquid (lotion) formulation (preferably W/O) which is suitable for topical application to the whole body. Each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

<u>(A) oil phase</u>		preferred	more preferred	most preferred
cetearyl octanoate	1 – 8 %	2 – 5 %	3.5 – 5 %	4.5 – 5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	6 – 20 %	8 – 15 %	12 – 15 %	14 – 15 %
polyglyceryl-3-diisostearate	1 – 4 %	1.5 – 3 %	1.75 – 2.25 %	1.9 – 2.1 %
polyglyceryl-2-dipolyhydroxystearate	2 – 6 %	3 – 5 %	3.5 – 4.5 %	3.75 – 4.25 %
ethylhexylglycerin	0 – 1 %	0 – 0.8 %	0.2 – 0.6 %	0.25 – 0.5 %
<u>(B) water phase</u>				
glycerin	0 – 6 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.25 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	1 – 1.4 %	1.2 – 1.3 %
sodium lactate	0.5 – 7 %	1 – 5 %	3 – 4.5 %	3.25 – 4.25 %
urea	0.5 – 12 %	0.5 – 10 %	3 – 7 %	4 – 6 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

It should be understood that the above-mentioned percentages or percentage ranges given for the ingredients of the formulations according to the invention may be subject to small variations (e.g., due to varying degrees of purity of the ingredients) without departing from the spirit of the invention.

However, the ingredients used for the dermatologic formulations of the invention should be of high quality and purity.

The hypoallergenic and non-irritant skin care formulations of the invention are suitable as emollients, for therapy or therapy support of eczematous and psoriatic skin, as well as for therapeutic daily skin care treatment of dry, sensitive skin.

Furthermore, the formulations of the invention may further comprise one or more of the ingredients selected from a sunscreen, a vitamin or vitamin analog, such as Vitamin E, Vitamin K, Calcipotriol, Tacalcitol, or a pharmaceutically active compound, such as corticoids, antimycotics, immunosuppressants, salicylic acid, alpha- or beta-hydroxy acids, or linolenic acid.

The group of corticoids may include but is not limited to hydrocortisone and derivatives thereof, such as methylprednisolone aceponate, diflucortolone valerate, fluocortolone pivalate / hexanoate / monohydrate, fluocortinbutyl, betamethasone and derivatives thereof, clobetasole, triamcinolone acetonide, dexamethasone, prednisolone, and clocortolone pivalate. The group of antimycotics may include but is not limited to ketoconazole, isoconazole, miconazole, and clotrimazole; and the group of immunosuppressants may include but is not limited to ascomycin and derivatives thereof, cyclosporine A, azathioprine, methotrexate, cyclophosphamide, and the like.

The invention furthermore provides a robust and easily applicable method of manufacturing the skin care formulations of the invention. Manufacturing of the skin care formulations is achieved by preparing the oil phase by melting the ingredients of the oil phase such as cetearyl octanoate, dicaprylyl ether, caprylic / capric triglyceride, polyglyceryl-3-diisostearate, polyglyceryl-2-dipolyhydroxystearate, petrolatum, cera alba, and ethylhexylglycerin, with stirring until all ingredients are completely melted. The ingredients chosen for the oil phase will depend on the oil phase that is desired, as described above.

For the water (aqueous) phase, purified water is heated in a separate vessel and the ingredients of the water phase such as magnesium sulfate, sodium lactate, lactic acid, and optionally glycerin, urea, and propylene glycol, are added depending upon the desired composition of the water phase (see above, for example). Such ingredients are dissolved with stirring and subsequently, the pH value of the resulting solution is adjusted with lactic acid to about 4.4 – 4.8. Both the oil and water phase are preferably heated to about 75 – 85°C during melting and dissolution, respectively.

Prior to the combination of the oil and the water phase, the oil phase is filtered through filter cartridges with 0.1 mm filter units for particulate filtration. Subsequently, the emulsion is prepared by transferring the melted oil phase as prepared above to the heated water phase and, while stirring and homogenizing, cooling the emulsion down under vacuum conditions, preferably about -0.6 to -0.9 bar, to room temperature.

Preferably, the oil phase is transferred into the water phase while stirring at about 40 min^{-1} at $75 - 85^{\circ}\text{C}$, cooled down to about $58 - 62^{\circ}\text{C}$ while stirring and homogenizing at 3000 min^{-1} , further cooled to about $38 - 42^{\circ}\text{C}$ while stirring and homogenizing at 4000 min^{-1} , and finally cooled down to about $23 - 27^{\circ}\text{C}$ while stirring. After the cooling process, the prepared semi-solid or semi-liquid W/O emulsions of the present invention can be discharged into appropriate containers.

The invention is further illustrated in the Examples. The Examples are not intended to limit the scope of the invention.

Example 1: Preparation of semi-solid formulation A

A semi-solid formulation according to the invention (designated Formulation A herein below) was prepared in a batch size of 50 kg using an ointment mixer and homogenizer (available under the trade name Becomix® RW 60 from Berents, Germany), equipped with a 60 L stainless steel pan, an infinitely variable anchor-type stirrer, homogenizer and process control system, a pH-meter, a stainless steel melting pan equipped with an infinitely variable stirrer, stainless steel ointment storage containers, and stainless steel sintered filter cartridges, 0.1 mm for particulate filtration.

For the preparation of the water phase, the ointment mixer/homogenizer was charged with 33.7 kg of purified water, 1.5 kg glycerin, 0.5 kg magnesium sulfate, and 0.992 kg sodium lactate and stirred (40 min^{-1}) at $80 \pm 2^{\circ}\text{C}$ until all components were completely dissolved. Subsequently, the pH value was checked and adjusted with 0.058 kg lactic acid to a pH of about 4.6.

The oil phase was prepared by charging the melting vessel with 1.5 kg petrolatum, 1.5 kg cetearyl octanoate, 1.5 kg dicaprylyl ether, 4.0 kg caprylic / capric triglyceride, 1.0 kg cera alba, 2.25 kg polyglyceryl-3-diisostearate, 0.75 kg polyglyceryl-2-dipolyhydroxystearate, and 0.15 kg ethylhexylglycerin and melted completely at 80 ± 2 °C while stirring until no unmelted material remained visible. Finally, the oil phase was filtered through stainless steel filter cartridges with 0.1 mm filter units for particulate filtration prior to the addition to the water phase.

The emulsion was subsequently prepared by transferring the oil phase to the water phase in the ointment mixer/homogenizer with stirring (40 min^{-1}) at 80 ± 2 °C. The resultant mixture was then cooled to 60 ± 2 °C while it was stirred and homogenized (3000 min^{-1} , cycle). The resulting emulsion was then further stirred and homogenized (4000 min^{-1} , cycle) during cooling to 40 ± 2 °C. Finally, stirring of the emulsion was continued until the emulsion had a temperature of 25 ± 2 °C. During the complete cool down process a vacuum of between -0.6 and 0.9 bar was applied.

The resulting cream was checked for homogeneity by microscopy for uniform appearance. After passing the homogeneity test, the product was discharged into bulk containers.

Example 2: Preparation of semi-solid formulation B

Formulation B was prepared as formulation A, with the exception that 4 kg of propylene glycol was added to the water phase and no ethylhexylglycerin was added to the oil phase.

Example 3: Preparation of semi-liquid formulation C

The semi-liquid formulation C was essentially prepared as formulations A and B in Examples 1 and 2. The differences in the manufacturing process are described below.

For the production of formulation C in a batch size of 50 kg, the ointment mixer / homogenizer was charged with 28.35 kg of purified water, 1.5 kg glycerin, 0.5 kg

magnesium sulfate, 1.867 kg sodium lactate, and 2.5 kg urea and stirred (40 min^{-1}) at $80 \pm 2^\circ\text{C}$ until all components were completely dissolved. Subsequently, the pH value was checked and adjusted with 0.633 kg lactic acid to a pH of about 4.2.

- 5 The oil phase was prepared by charging the melting vessel with 2.5 kg cetearyl octanoate, 1.5 kg dicaprylyl ether, 7.5 kg caprylic/capric triglyceride, 1.0 kg polyglyceryl-3-diisostearate, 2.25 kg polyglyceryl-2-dipolyhydroxystearate, and 0.15 kg ethylhexyl-glycerin and melted completely at $80 \pm 2^\circ\text{C}$ while stirring until no unmelted material remained visible.

10 After particulate filtration, both phases were combined to form an emulsion as described in Example 1. After passing the homogeneity test, the resulting lotion was discharged into bulk containers.

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Example 4: Microbiological/ physicochemical stability

The formulations A, B, and C as prepared in Examples 1 to 3 were subjected to the following stability tests:

- 20 a) Storage at 4°C , 25°C , 30°C , 40°C , 50°C at ambient humidity over 5 months
- b) $-4^\circ\text{C} / 50^\circ\text{C}$ cycle test over 2 weeks
- c) Microbiological challenge test according to USP (United States Pharmacopeia) requirements

25 The formulations were packaged in PE containers (HDPE/LDPE) in batch sizes of 2 – 25 kg and tested for parameters such as pH-value, viscosity (abs.), microscopic and macroscopic picture, content of urea (formulation C), and compatibility with the container material.

30 The test results showed that formulations A – C of Examples 1 – 3 are physicochemically stable under all tested conditions and meet the microbiological stability requirements of the USP.

Example 5: Sensitization and Irritation Risk (HRIPT-Test)

- A human repeated insult patch test (HRIPT) was carried out as a 40-days randomized, controlled, double-blind study to assess the sensitizing and irritating potential of the dermatological skin care formulations of the invention. The study was started with 58 healthy volunteers of either sex between 18 and 65 (ITT-cases: n= 58), however, 3 volunteers dropped out and 55 volunteers completed the study (VC-cases: n= 55).
- 10 In the induction phase (day 1 – 20), the volunteers were subjected to nine occlusive treatments for 24 hours with 75 µl of the test formulations as prepared in Examples 1 – 3 applied to their backs on days 1, 3, 5, 8, 10, 12, 15, 17, 19. Untreated test fields without application of a test formulation were used as a concurrent control. Skin reactions were evaluated 24 hours (1/2 hour after removal of test chambers; on days 2, 4, 6, 9, 11, 13, 16, 18, 20; nine readings) and 48 hours after the application of occlusive treatments on the backs of the volunteers (1/2 hour after removal of test chambers on days 3, 5, 10, 12, 17,19; six readings) by a visual 6-point-score.

Visual 6-point-score	
0	Negative/ no reaction
0.5	Equivocal erythema
1	Erythema
2	Erythema and induration (edema)
3	Erythema, induration (edema) and vesicles
4	Erythema, induration (edema) and bullae and/or spreading

- 20 The mean cumulative irritation index (M.C.I.I.) was calculated for the 24 hours readings (M.C.I.I./ 24 h.) and for the 48 hours readings (M.C.I.I./ 48 h.).

B

After the treatment-free interval (15 days; days 21-35; no treatment), an occlusive challenge application of the test formulations on yet untreated test sites on the backs of the volunteers was done for 24 hours. The test formulations were evaluated 24 h, 48 h, 72 h and 96 h after the application by the same visual 6-point score (challenge phase; 5 days, days 36-40).

Results:

Sensitization: No case of sensitization occurred in both ITT- and VC-population.

Irritation: No significant irritation potential in comparison to the empty untreated test field could be observed in both ITT- and VC-population.

Furthermore, no adverse events or serious adverse event related to the test formulations was observed during the course of the study.

Example 6: Irritation Potential

The primary objective of this study was to evaluate the cutaneous tolerability of the skin care formulations of the invention over a 4-weeks period when used in the intended way (application twice daily to face or body, respectively) in the intended patient/consumer group having dry and sensitive skin. The secondary objectives of this study were to evaluate the irritation potential of the test formulations A and B when used around the eyes, to evaluate the hydrating effect of all test formulations as measured by corneometry, to evaluate the volunteer's general cosmetic acceptance of all test formulations, and finally to evaluate the cosmetic acceptance of the test formulations A and B as make-up foundations.

The study was designed as a single center, randomized study; double-blinded with interindividual comparison of treatments between the test formulations A, B, and comparative commercially available products for facial application and between test formulation C and comparative commercially available products for body application, and was performed for 28 consecutive days.

Healthy volunteers of either sex between 18 and 65 years old meeting specific inclusion/exclusion criteria with dry skin proven by low corneometer values (≤ 70) were chosen for this study. In addition, 50% of the volunteers were healthy individuals with atopic diathesis according to the atopy score of Diepgen without history for atopic dermatitis. The other 50% of the volunteers were without atopic diathesis. All volunteers in all treatment groups treated face and body twice daily at home over 28 consecutive days with the respective test formulations.

10 For the measurement of the hydrating effects of the test formulations for facial application, corneometry of both cheek bones was performed on days 1 and 29. For the test formulation for body application, corneometry of both anterior lower legs was performed on screen and on days 1 and 29.

15 A clinical assessment was performed at screen and on days 1, 8, 15 and 29 using a visual 5-point score (no / doubtful / slight / moderate / severe signs of irritation, erythema and/or scaling). Out of the results of the visual 5-point score an irritation product profile was created with four irritation groups being the primary variable of this study. Subjective symptoms were asked on days 8, 15 and 29 using a 5-point score for subjective evaluation
20 (no / doubtful / slight / moderate / severe sensation of stinging / burning / pruritus with specification in case of any positive answer). Additionally, an ophthalmological examination investigating fore- and background of the eyes as well as the conjunctival mucosa and subjective ophthalmological symptoms using a 5-point score for subjective ophthalmological symptoms took place on days 1 and 29.

25

Additionally, a questionnaire concerning the sensorial profile and overall cosmetic acceptance (parameters: distribution/spreading, absorption, feeling on the skin, stickiness, greasiness, oily shine, odor, and color; evaluation on a 5-point scale) was filled in by the volunteers on day 29.

30

Results:

Table 1 summarizes the hydration effect as measured by corneometry of three embodiments of the invention (formulations A, B and C) in comparison to a reference product.

Table 1: Measurement of Hydration Effect by Corneometry

Hydration effect (Corneometry)	Hydration improvement on Day 29 (in %) subgroup I (atopic subjects)	Hydration improvement on Day 29 (in %) subgroup II (non-atopic subjects)	Hydration improvement on Day 29 (in %) subgroup I + II
Formulation A (cream)	43.1	21.0	32.1
Formulation B (cream)	31.2	39.1	35.1
Formulation C (milk)	38.6	45.7	42.2
Reference product [§]	37.1	22.2	29.7

measured by corneometry of both cheek bones (Formulations A and B) and both anterior lower legs (Formulation C), respectively.

[§] commercially available W/O emulsion

In sum, application of the test formulations A, B and C for 28 days resulted in a significant hydration improvement between 32 % and 42 %, averaged over both subgroups (atopic and non-atopic subjects).

The results of the cutaneous tolerability study of formulations A, B, and C are summarized in Table 2. Tables 2 (a) and (b) show the results of the dermatological and ophthalmological investigations, respectively.

Table 2: Results of Tolerability Study (Irritation Potential)**Table 2 (a): Dermatological Investigation:**

Dermatological Investigation (ITT)	Face Formulations		Body Formulation
	Formulation A	Formulation B	Formulation C
(1) Irritation profile: objective signs	1/20 patients: moderate irritation and stop of treatment on day 14	1/20 patients: slight irritation; reduction of treatment dose	-
(2) Partial or transient stop of treatment related or possibly related to test formulation			-
Objective signs of irritation: (1) + (2)	5%	5%	-
(3) Irritation profile, subjective symptoms	1/20 patients: slight pruritus	2/20 patients: slight stinging 1/20 patients: slight pruritus	2/19 patients: slight stinging
Subjective signs of irritation: (3) moderate or severe reactions	-	-	-
Mean Sum of irritation score	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00
Conclusion	Very good irritation profile	Excellent irritation profile	Excellent irritation profile

Table 2 (b): Ophthalmological Investigation

Ophthalmological Investigation	Face Formulations		Body Formulation
	Formulation A	Formulation B	Formulation C
<i>Ophthalmologic objective symptoms</i>	1/20 patients: moderate conjunctival allergy left eye and mild conjunctival allergy right eye*	-	<i>body formulation not tested around the eyes</i>
<i>Ophthalmologic subjective symptoms</i>	1/20 patients: moderate subjective symptoms*	1/20 patients: slight itching tearing of left eye*	
<i>Application interrupted or stopped due to ophthalmological symptoms</i>	-	-	
Conclusion	Excellent tolerability of formulations when applied around the eyes		

* Subsequent studies demonstrated that the above symptoms were not caused by Formulations A and B.

As evident from the tabulated results, all tested dermatologic formulations of the invention exhibited a very good or even excellent irritation profile.

Additionally, the results of the questionnaire concerning the cosmetic acceptance of formulations A, B, and C are depicted in Tables 3 (a) –(i). The following parameters were tested: overall cosmetic quality (Table 3(a)); distribution / spreading (Table 3(b)); absorption (Table 3(c)); feeling on the skin (Table 3(d)); stickiness (Table 3(e)); greasiness (Table 3(f)); oily shine (Table 3(g)); odor (Table 3 (h)); color (Table 3 (i)).

Table 3: Results of sensory assessment tests

All values are given in % of volunteers.

Table 3 (a): Overall opinion of the cosmetic qualities of formulations A - C

Overall opinion	excellent	very good	good	acceptable	bad	no comment
Formulation A (cream)	16	42	32	5	5	0
Formulation B (cream)	15	10	45	5	10	15
Formulation C (lotion)	26	16	37	5	11	5

Table 3 (b): Distribution / Spreading

Distribution / Spreading	very easy	easy	moderately easy	difficult	very difficult
Formulation A (cream)	16	26	26	5	26
Formulation B (cream)	30	0	30	20	20
Formulation C (lotion)	11	5	16	11	58

5 **Table 3 (c): Absorption**

Absorption	very quick	quick	quite quick	slowly	very slowly	no comment
Formulation A (cream)	26	11	26	11	26	0
Formulation B (cream)	30	15	10	15	25	5
Formulation C (lotion)	21	0	11	21	47	0

Table 3 (d): Feeling on the skin

Feeling on the skin	too light	light	just right	heavy	too heavy
Formulation A (cream)	11	5	26	21	37
Formulation B (cream)	10	5	30	25	30
Formulation C (lotion)	5	5	11	21	58

Table 3 (e): Stickiness

Stickiness	not at all sticky	very few sticky	somewhat sticky	quite sticky	sticky
Formulation A (cream)	26	5	37	11	21
Formulation B (cream)	15	10	45	15	15
Formulation C (lotion)	0	0	26	32	42

Table 3 (f): Greasiness

Greasiness	not at all greasy	very few greasy	somewhat greasy	quite greasy	greasy
Formulation A (cream)	11	5	32	42	11
Formulation B (cream)	15	0	20	55	10
Formulation C (lotion)	5	5	26	63	0

5 Table 3 (g): Oily shine

Oily shine	leaves no oily shine	leaves a very light oily shine	leaves a light oily shine	leaves an oily shine	leaves a very oily shine	No comment
Formulation A (cream)	21	5	21	37	16	
Formulation B (cream)	15	0	25	20	40	
Formulation C (lotion)	16	0	11	37	32	5

Table 3 (h): Odor

Odor	no	yes, very light	yes, light	yes, moderate	yes, strong	yes, very strong
Formulation A (cream)	53	16	21	0	5	5
Formulation B (cream)	40	35	15	5	5	0

Formulation C (lotion)	58	21	16	5	0	0
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Table 3 (i): Color

Color	very pleasant	pleasant	unpleasant	I don't care	no comment
Formulation A (cream)	16	53	16	16	0
Formulation B (cream)	20	45	15	20	0
Formulation C (lotion)	16	53	26	5	0

5 Example 7: Phototoxicity

In order to assess the phototoxic potential of the dermatologic skin care formulations of the invention, the semi-solid formulations of example 1 and 2 were tested in a phototoxicity study running for 5 consecutive days. The study was designed as a single center, randomized, double-blind study with intraindividual comparison of treatments and inter-individual comparison of treatments for the test formulations A and B. 12 healthy volunteers of either sex between 18 and 50 years old meeting specific inclusion/ exclusion criteria were enrolled in the study. 50 µl of each test formulation was applied under occlusive conditions in duplicate on subject's back on days 1 for 24 hours. One duplicate test field without application of a formulations (empty test chamber with/without UV-radiation) was used as a control.

On day 1 and 2, the minimal erythema dose (MED) was assessed by irradiation of six small test fields with UVA/B on the upper back of the volunteer. The test chambers with the test formulations in duplicate were applied on day 1 to the designated test fields on both sides of the mid back of the volunteers. On day 2, the test chambers were removed after 24 hours and the test fields ($20 \text{ J/cm}^2 \text{ UVA} + 0.75 \times \text{MED UVA+UVB}$) were irradiated on the left side of the mid back. The skin reactions were evaluated after one hour (day 2), after 24 hours (day 3), after 48 hours (day 4) and after 72 hours (day 5) using a 5-point visual score:

Visual 5-point score	
0	No erythema
0.5	Equivocal erythema (barely perceptible erythema with no clearly defined border)
1	Mild but definite erythema with clearly defined border (MED)
2	Moderate, clearly defined erythema
3	Severe erythema, with or without infiltration
4	Severe erythema with vesicles or bullous reaction

The number of volunteers who experienced a phototoxic reaction during the study determined the phototoxic potential of the test formulations.

- 5 **Results:** No case of phototoxicity could be observed with the dermatologic formulations A and B during the study in the test population.

Example 8: Photo-Sensitization Risk

- 10 The primary objective of this study was to evaluate the photosensitizing potential of the dermatologic formulations of the invention in a population of n=25 healthy volunteers of either sex between 18 and 65 years with Fitzpatrick's skin type I, II, or III meeting specific inclusion/ exclusion criteria using the modified method of Kaidbey & Kligman (Kaidbey & Kligman, 1980, *Contact Dermatitis* 6, 161-169). The secondary objective of this study was
15 to evaluate the sensitization potential of the formulations.

- The study was designed as a single center, randomized, double-blind study with intraindividual comparison of treatments and interindividual comparison of treatments for the test formulations including formulations A and B (cream) and was performed for 6
20 consecutive weeks. As a control, untreated test fields without application of test formulations were included into the study.

During the induction phase one series of test plasters with all test formulations and one empty field was fixed on the left sides of the backs. During the challenge phase two series of test plasters were fixed on each side of the back. Only the right side of the back was irradiated. Allocation of test formulations to test fields was identical for each volunteer during induction and challenge phase. For each application, 50 µl of the test formulation was applied under occlusive conditions on volunteers' backs on days 1, 4, 8, 11, 15, 18, and 36.

The MED of each subject was determined by irradiating increasing doses of UVA/UVB/ with a solar simulator on previously selected sites of the volunteers back. Scoring was performed 24 hours after the irradiation. The MED is the smallest dose (mJ/cm²) needed to induce a visible, clearly delineated erythema.

In the induction phase (20 days; day 1-20), six occlusive applications of one series of test formulations were done for 24 hours on the left side of the backs of volunteers on days 1, 4, 8, 11, 15, 18. After 24 h, the occlusive treatments were removed and all test fields were consecutively exposed to 3 x MED UVA/UVB with a solar simulator on days 2, 5, 9, 12, 16, and 19. The results were evaluated 24 h after the irradiation by a 6-point visual score.

In the challenge phase (5 days; day 36-40) after the treatment-free interval (15 days; day 21-35), occlusive application of two series of test formulations on yet untreated sites on both sides of the backs of the volunteers were performed for 24 hours (challenge application). Consecutively, the test fields were exposed on the right side of the backs to 10 J/cm² UVA plus 0.75 x MED (UVA/UVB) (challenge irradiation on day 37). The results were evaluated one hour after the challenge irradiation and additionally 24 h, 48 h and 72 h after challenge irradiation by a 6-point visual score.

The following 6-point visual score was used during induction and challenge phase:

Visual 6-point-score	
0	No erythema
0.5	Equivocal erythema
1	Definite erythema with clearly defined border (MED)
2	Erythema with infiltration/ papules
3	Erythema with vesicles or bullous reaction
4	Erythema with eroded bullous reaction and/or raised spreading reaction beyond the borders of the patch site

Results: No case of photosensitization could be observed under the above-described conditions for the dermatological formulations A and B of Example 1 and 2 (facial formulations) in any of the volunteers.

Claims:

1. A hypoallergenic and non-irritant skin care formulation, wherein the formulation:
 - a) is free from fragrances, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins; and
 - 5 b) comprises a water phase dispersed in an oil phase, wherein the oil phase comprises cetearyl octanoate, dicaprylyl ether, caprylic / capric triglyceride, polyglyceryl-3-diisostearate and polyglyceryl-2-dipolyhydroxystearate.
- 10 2. The skin care formulation according to claim 1, the formulation having a total number of ingredients that is less than 15.
3. The skin care formulation according to claims 1 – 2, wherein the water phase comprises the ingredients purified water, magnesium sulfate, lactic acid and sodium lactate.
- 15 4. The skin care formulation according to claims 1 – 3, wherein the water phase further comprises glycerin.
- 20 5. The skin care formulation according to claims 1 – 4, wherein the oil phase further comprises ethylhexylglycerin.
6. The skin care formulation according to claims 1 – 4, wherein the oil phase of the formulation further comprises petrolatum and cera alba.
- 25 7. The skin care formulation according to claim 6, wherein the oil phase further comprises ethylhexylglycerin.
8. The skin care formulation according to claim 6, wherein the water phase further comprises propylene glycol.

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9. The skin care formulation according to claims 1 - 5, wherein the water phase further comprises urea.

- 5 10. A semi-solid skin care formulation comprising the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

- 10 a) petrolatum: 2 - 5 %
b) cetearyl octanoate: 2 - 5 %
c) dicaprylyl ether: 1 - 3 %
d) caprylic / capric triglyceride: 5 - 10 %
e) cera alba: 1.0 - 2.5 %
f) polyglyceryl-3-diisostearate: 4 - 5 %
g) polyglyceryl-2-dipolyhydroxystearate: 1 - 2 %
15 h) ethylhexylglycerin: 0 - 0.8 %

(2) water phase:

- 20 a) glycerin: 0 - 5 %
b) magnesium sulfate: 0.5 - 1.5 %
c) lactic acid : 0.05 - 1.5 %
d) sodium lactate: 1 - 5 %
e) purified water: add to 100 %

- 25 11. A semi-solid skin care formulation, wherein the formulation comprises the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

- 30 a) petrolatum: 2 - 5 %
b) cetearyl octanoate: 2 - 5 %
c) dicaprylyl ether: 1 - 3 %

- | | |
|--|-------------|
| d) caprylic / capric triglyceride: | 5 – 10 % |
| e) cera alba: | 1.0 – 2.5 % |
| f) polyglyceryl-3-diisostearate: | 4 – 5 % |
| g) polyglyceryl-2-dipolyhydroxystearate: | 1 – 2 % |

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(2) water phase:

- | | |
|-----------------------|--------------|
| a) glycerin: | 0 – 5 % |
| b) magnesium sulfate: | 0.5 – 1.5 % |
| c) lactic acid : | 0.05 – 1.5 % |
| d) sodium lactate: | 1 – 5 % |
| e) propylene glycol: | 5 – 10 % |
| f) purified water: | add to 100 % |

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- 15 12. A semi-liquid skin care formulation comprising the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

- | | |
|--|-----------|
| a) cetearyl octanoate: | 2 – 5 % |
| b) dicaprylyl ether: | 1 – 3 % |
| c) caprylic / capric triglyceride: | 8 – 15 % |
| d) polyglyceryl-3-diisostearate: | 1.5 – 3 % |
| e) polyglyceryl-2-dipolyhydroxystearate: | 3 – 5 % |
| f) ethylhexylglycerin: | 0 – 0.8 % |

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(2) water phase:

- | | |
|-----------------------|--------------|
| a) glycerin: | 0 – 5 % |
| b) magnesium sulfate: | 0.5 – 1.5 % |
| c) lactic acid : | 0.05 – 1.5 % |
| d) sodium lactate: | 1 – 5 % |
| e) urea: | 0.5 – 10 % |
| f) purified water: | add to 100 % |

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13. The skin care formulation according to any of claims 1 – 12, wherein the formulation further comprises one or more pharmaceutically active compounds, vitamins or vitamin analogs, and/or sunscreens.

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14. The skin care formulation according to claim 13, wherein the pharmaceutically active compound is a corticoid, an antimycotic, salicylic acid, an alpha- or beta-hydroxy acid, and/or linolenic acid; wherein the vitamin is Vitamin E, or Vitamin K; and wherein the vitamin analog is Calcipotriol, or Tacalcitol.

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15. The skin care formulation according to any of claims 1 – 14 for use in the prophylaxis and treatment of dry, sensitive skin or the therapy of eczematous skin and psoriatic skin.

- 15 16. A method of manufacturing a hypoallergenic and non-irritant skin care formulation comprising the steps of:

- a) preparing an oil phase by melting the ingredients of the oil phase as defined in any one of claims 1, 5, 6, 7, or 10 – 12;
- b) preparing a water phase by heating purified water and dissolving therein the ingredients of the water phase as defined in any of claims 3, 4, 8, or 10 – 12 while stirring and adjusting the pH value of the resulting solution with lactic acid to about 4.4 – 4.8;
- c) preparing a water-in-oil emulsion by transferring the melted oil phase from step (a) to the heated water phase of step (b) and, while stirring and homogenizing, cooling the emulsion down to room temperature while applying a vacuum of about -0.6 to -0.9 bar.

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17. The method of claim 16, wherein step (a) and step (b) are performed at a temperature of about 75 – 85°C and wherein step (c) comprises the steps of transferring the oil phase of step (a) into the water phase of step (b) while stirring at

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about 40 min⁻¹ at 75 – 85°C, cooling the emulsion down to about 58 – 62°C while stirring and homogenizing at 3000 min⁻¹, cooling the emulsion further down to about 38 – 42°C while stirring and homogenizing at 4000 min⁻¹, cooling the emulsion further down to about 23 – 27°C while stirring, and discharging the emulsion into appropriate containers.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14825

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DE 19843876	A	13-04-2000	DE 19843876 A1	13-04-2000
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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	DE 198 43 876 A (COGNIS DEUTSCHLAND GMBH) 13 April 2000 (2000-04-13) table 1	1-17
A	EP 0 847 750 A (BEIERSDORF AG) 17 June 1998 (1998-06-17) examples 1-16	1-17
A	ANOM.: "Final Report on the safety assessment of Cetearyl Octanoate" J. AMERICAN COLLEGE OF TOXICOLOGY, vol. 1, no. 4, 1982, pages 81-90, XP000982324 the whole document	1-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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(54) Title: **HYPOALLERGENIC AND NON-IRRITANT SKIN CARE FORMULATIONS**

(57) Abstract: The invention provides novel hypoallergenic and non-irritant medical skin care formulations being water-in-oil emulsions. The formulations are free from ingredients with a known allergenic potential, such as fragrances, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins, thus being particularly suitable for patients with sensitive dry skin. The skin care formulations of the invention are useful in the prophylaxis and treatment of dry, sensitive skin or in the therapy or therapy support of eczematous or psoriatic skin and exhibit favorable sensorial properties. The invention furthermore provides a method of manufacturing the novel hypoallergenic and non-irritant skin care formulations.

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Hypoallergenic and non-irritant skin care formulations

Field of the Invention

This invention relates to hypoallergenic and non-irritant skin care formulations. The formulations of the invention are particularly suitable for medical applications such as for treating dry, sensitive skin and for therapy of skin conditions such as eczema and psoriasis. The formulations of the invention are compliance-friendly and superior to previously known formulations claiming to be hypoallergenic and non-irritant.

Background of the Invention

Human skin acts as a barrier and protective layer against chemical, physical and mechanical insults. The primary function of the skin's outer layer—the horny layer—is to prevent loss of water and vital substances into the environment while keeping noxious exogenous materials from penetrating to living tissue. The person skilled in the art refers to the outer horny layer as the *stratum corneum* (SC). Other functions of the SC include regulation of homeostatic mechanisms to assure steady-state conditions in the face of a changing environment, mechanisms of repair after disruption of the barrier by disease or exogenous insults and the presence of anti-bacterial substances to protect against infection. In order to fulfill these functions, the SC needs to be hydrated and flexible.

Complicated mechanisms in the skin maintain the essential hydration state of the SC. However, many factors work to compromise the SC barrier and increase the rate of water loss. Exposure to harsh conditions, including cold, dry winter weather, frequent washing with soap and hot water, exposure to surfactants or irritating chemicals or solvents may cause skin dryness. Apart from external factors provoking dry skin conditions, several diseases are known that are characterized by an abnormal condition or behavior of the SC. Examples of these diseases are atopic dermatitis, psoriasis and ichthyosis.

The SC sheds clusters of cells known as corneocytes from the surface of the skin while continuously replenishing them from underlying layers. This process is usually imperceptible due to the small size of the clusters, but in dry skin, the larger aggregates of

these cells are shed as scales or flakes. Dry skin is characterized by a rough, dry feeling and flaky appearance. It may itch and become red and irritated, and persons suffering from very dry skin^V (xerosis) may scratch affected areas repeatedly. If such conditions are untreated, severely dry skin may crack and bleed. Accumulation of thick brittle scales may occur such as in psoriasis and various forms of ichthyosis.

Skin moisturizers are used to help prevent skin from becoming dry or to return dry skin to its normal condition. Several compounds are known to act as skin moisturizers or humectants. Among these are glycerol (glycerin), urea, petrolatum^V (petroleum jelly), polyethylene glycols (PEGs), lanolins (wool wax), lactic acid (lactate), and ceramides. In skin care products, these ingredients are formulated together with a large variety of other ingredients used for maximizing efficacy, stability and shelf life. For skin care products, the subjective impressions of the user are particularly important. Thus, ingredients for improving subjective properties such as stickiness/greasiness, distribution/spreading, absorption, odor, or color are also added. Typically, skin care products are comprised of about 20–50 different ingredients, since it is the experience of the personal skilled in the art that favorable results may not be achieved by formulations with fewer ingredients.

The ingredients of skin care formulations are generally combined to form an emulsion, since they consist of hydrophobic and hydrophilic ingredients. In principle, two basic types of emulsions are possible. In an oil-in-water (O/W) emulsion, the oil phase forms the discontinuous phase, whereas in a water-in-oil (W/O) emulsion, the water phase represents the discontinuous phase.

Most skin care products are formulated as O/W emulsions. O/W emulsions are usually preferred for cosmetics, due to their favorable cosmetic properties that are pleasing for consumers. An O/W emulsion however represents a trade off in favor of such user-pleasing properties, since O/W-emulsions are generally less effective than W/O emulsions in treating or ameliorating dry skin conditions.

It has been suggested that W/O emulsions are suitable as an adjunctive therapy in the treatment of psoriasis, thus providing a^V steroid-sparing effect (Watsky et al., 1992, *Cutis*

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50, 1992). In U.S. Patent No. 5,561,166, Sattler et al., a W/O composition containing urea and salts of lactic acid for the treatment of dry skin was disclosed. Additionally, U.S. Patent No. 5,552,147 discloses cosmetic compositions containing alpha hydroxy carboxylic acids dispersed in petroleum jelly with the aid of a phosphatide.

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A common problem associated with skin care products is that they cause adverse effects in consumers or patients. Such unwanted effects include irritation (subjective and objective), allergic contact dermatitis, photocontact dermatitis, and immediate contact reactions ("*Dry Skin and Moisturizers: Chemistry & Function*", p. 403, Eds. Loden & Maibach, 2000). In this context, it should be understood that irritant reactions are distinct to allergenic reactions due to their different characteristics and/or mode of action. Established techniques such as patch testing are known to those skilled in the art and can be used to differentiate between the two types of reaction (see e.g., "*Unwanted effects of cosmetics and drugs used in dermatology*", pp. 6-10, Eds. de Groot, Weyland and Nater, Elsevier 1994).

15

The most frequently observed side effect is allergic contact dermatitis. This reaction is usually caused by fragrances and preservatives present in these products. Another origin of allergic reactions are moisturizers such as lanolin and its derivatives, emulsifiers such as cocamidopropyl betaine, and emollients.

20

Although many of the ingredients typically used in skin care formulations have a known irritation or allergenic sensitization potential and the rate of allergenic reactions in consumers or patients has increased dramatically over the last few years, these ingredients are still used in the majority of products in the skin care market of today. Several skin care formulations claim to be low in certain allergens and/or irritants. U.S. Patent No. 5,863,546 discloses cosmetic compositions, which differ significantly from the skin formulations of the invention, that exclude certain allergens and irritants.

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30 The prior art has failed to provide a skin care formulation that avoids irritant and allergenic ingredients but retains favorable properties, in particular in the field of medical skin care. This may be attributed to the fact that strictly avoiding such ingredients undermines other

desired properties such as effective moisturizing of dry skin, stability of the formulation and favorable sensory attributes from the point of the view of the patient/consumer.

Accordingly, there is a need for a hypoallergenic and non-irritant skin care formulation that effectively moisturizes dry, sensitive skin while at the same time exhibiting physical/microbiological stability and meeting the subjective aesthetic expectations of the patient/consumer.

10 **Object and Summary of the Invention**

It is an object of the present invention to solve the problems associated with available and known skin care formulations by providing a hypoallergenic and non-irritant skin care formulation. Aside from being hypoallergenic and non-irritant, the formulations of the invention effectively moisturize dry, sensitive skin and are stable and pleasing to the patient/consumer. The formulations of the invention are suitable for medical skin care, such as for the therapy or therapy support of psoriasis and eczema.

The formulations of the invention are free from ingredients such as perfumes or perfume substitutes (fragrances), preservatives, colorings, plant extracts, polyethylene glycols (PEGs), cetylstearyl alcohol, lanolin alcohols, lower alcohols, proteins and other substances with known allergenic potential, thus being particularly suitable for patients with sensitive skin. However, it is noted that the term "free from ingredients with known allergic potential" is intended to mean that such substances are not purposefully included in the formulations, although they might be present in very limited amounts, e.g. as a contaminant of other ingredients. Since the allergenic and/or irritant potential of the ingredients is generally known to be dependent on their concentration, it should be understood that the presence of very limited amounts of such ingredients is still meant to be within the scope of the present invention.

The formulations of the invention comprise a water phase dispersed in an oil phase. In this embodiment, the oil phase may comprise cetearyl octanoate, dicaprylyl ether,

caprylic / capric triglyceride, polyglyceryl-3-diisostearate and polyglyceryl-2-dipolyhydroxystearate.

In one aspect of the invention, the formulations have relatively few ingredients, preferably
5 less than 15, most preferably 12 or 13 ingredients.

In another aspect of the invention, the water phase of the formulations comprises the ingredients purified water, magnesium sulfate, lactic acid and sodium lactate. Additionally, the water phase may further comprise glycerin.

10

In one embodiment, the oil phase of the formulation may further comprise petrolatum and cera alba. Additionally, the oil phase may comprise ethylhexylglycerin or, alternatively, the water phase may further comprise propylene glycol.

15 In a second embodiment, the oil phase may further comprise ethylhexylglycerin. In this second embodiment, the water phase may further comprise urea.

The invention furthermore provides a method of manufacturing the hypoallergenic and non-irritant skin care formulations of the invention. It also provides formulations further
20 comprising one or more pharmaceutically active compounds, vitamins or vitamin analogs, and/or a sunscreen, as well as formulations for use in the prophylaxis and treatment of dry, sensitive skin or in the therapy of eczematous or psoriatic skin.

It is another object of the invention to provide a method for the prophylaxis and treatment
25 of dry, sensitive skin or for therapy support of eczematous skin and psoriatic skin by topically administering a therapeutically effective amount of the dermatological skin care formulations of the present invention.

30 Detailed Description of the Invention

The invention provides hypoallergenic and non-irritant skin care formulations having superior properties. The formulations of the invention, exemplary embodiments of which

are described in more detail below, are particularly suitable for medical skin care and for the treatment of dry, sensitive skin. Despite being free from such ingredients as perfumes or perfume substitutes, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins, the formulations of the invention
5 unexpectedly retain many desirable properties.

Although many of the ingredients commonly used in skin care formulations are not present, the skin care formulations of the invention are highly effective with maximal skin tolerance. For the formulations, the inventor chose raw materials with a proven skin
10 tolerance and a high physicochemical and microbiological stability. Focusing on the properties of the individual ingredients, the inventor selected a mixture of skin lipids on the basis of sensorial properties, tactility and polarity. Furthermore, in order to overcome the problems of the prior art, substances with known allergenic or irritant potential were eliminated and only selected ingredients, preferably possessing multifunctional properties,
15 and modern types of biodegradable emulsifiers are employed. These formulations exhibit a high degree of dispersity and are suitable for application in climate zone IV.

Though suitable for medical use, the skin care formulations of the invention have favorable cosmetic properties, such as excellent absorption, lack of stickiness, scent, and oily shine.
20 This is evidenced by the results of sensory assessment studies performed with several embodiments of the invention (see Table 3).

The formulations of the invention furthermore exhibit excellent physical/microbiological stability (see Example 4) and fulfill the requirements of the cosmetic directives of the
25 European Union and the United States. The formulations are physicochemically stable and meet the United States Pharmacopeia (USP) requirements in terms of microbiological stability. Although free of any preservatives, a shelf life of at least 2 years can be expected for the formulations of the invention.

30 In a preferred embodiment of the present invention, the skin care formulation is in the form of a semi-solid formulation (cream), which is particularly suitable for topical application to the face. Such a formulation is preferably a W/O emulsion.

The following table lists the ingredients of such a preferred formulation of the invention wherein each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

5

<u>(A) oil phase</u>		preferred	more preferred	most preferred
petrolatum	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
cetearyl octanoate	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
cera alba	0.5 – 4 %	1.0 – 2.5 %	1.5 – 2.5 %	1.75 – 2.25 %
polyglyceryl-3-diisostearate	3 – 6 %	4 – 5 %	4.25 – 4.75 %	4.4 – 4.6 %
polyglyceryl-2-dipolyhydroxystearate	0.5 – 3 %	1 – 2 %	1.25 – 1.75 %	1.4 – 1.6 %
ethylhexylglycerin	0 – 1 %	0 – 0.8 %	0.2 – 0.6 %	0.25 – 0.5 %
<u>(B) water phase</u>				
glycerin	0 – 7 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.2 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	0.05 – 0.5 %	0.05 – 0.25 %
sodium lactate	0.5 – 6 %	1 – 5 %	1.5 – 2.5 %	1.6 – 2.0 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

In a second preferred embodiment, the semi-solid (cream) formulation comprises the following ingredients, wherein each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

10

<u>(A) oil phase</u>		preferred	more preferred	most preferred
petrolatum	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
cetearyl octanoate	1 – 6 %	2 – 5 %	2.5 – 4 %	2.75 – 3.5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
cera alba	0.5 – 4 %	1.0 – 2.5 %	1.5 – 2.5 %	1.75 – 2.25 %
polyglyceryl-3-diisostearate	3 – 6 %	4 – 5 %	4.25 – 4.75 %	4.4 – 4.6 %
polyglyceryl-2-dipolyhydroxystearate	0.5 – 3 %	1 – 2 %	1.25 – 1.75 %	1.4 – 1.6 %
<u>(B) water phase</u>				
glycerin	0 – 7 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.2 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	0.05 – 0.5 %	0.05 – 0.25 %
sodium lactate	0.5 – 6 %	1 – 5 %	1 – 3 %	1 – 2.5 %
propylene glycol	4 – 12 %	5 – 10 %	7 – 9 %	7.5 – 8.5 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

Preferably, the above formulation is a W/O emulsion. It is also particularly suitable for application to the face.

In a third preferred embodiment of the invention, the skin care formulation is in the form of a semi-liquid (lotion) formulation (preferably W/O) which is suitable for topical application to the whole body. Each ingredient may be present in an amount independently of the amount of the other according to the ranges given in the table below and expressed as percent by weight (% w/w).

27

<u>(A) oil phase</u>		preferred	more preferred	most preferred
cetearyl octanoate	1 – 8 %	2 – 5 %	3.5 – 5 %	4.5 – 5 %
dicaprylyl ether	1 – 5 %	1 – 3 %	2 – 3 %	2.5 – 3 %
caprylic / capric triglyceride	6 – 20 %	8 – 15 %	12 – 15 %	14 – 15 %
polyglyceryl-3-diisostearate	1 – 4 %	1.5 – 3 %	1.75 – 2.25 %	1.9 – 2.1 %
polyglyceryl-2-dipolyhydroxystearate	2 – 6 %	3 – 5 %	3.5 – 4.5 %	3.75 – 4.25 %
ethylhexylglycerin	0 – 1 %	0 – 0.8 %	0.2 – 0.6 %	0.25 – 0.5 %
<u>(B) water phase</u>				
glycerin	0 – 6 %	0 – 5 %	2 – 4 %	2.5 – 3.5 %
magnesium sulfate	0.25 – 2 %	0.5 – 1.5 %	0.8 – 1.2 %	0.9 – 1.1 %
lactic acid	0 – 2 %	0.05 – 1.5 %	1 – 1.4 %	1.2 – 1.3 %
sodium lactate	0.5 – 7 %	1 – 5 %	3 – 4.5 %	3.25 – 4.25 %
urea	0.5 – 12 %	0.5 – 10 %	3 – 7 %	4 – 6 %
purified water	add to 100 %	add to 100 %	add to 100 %	add to 100 %

It should be understood that the above-mentioned percentages or percentage ranges given for the ingredients of the formulations according to the invention may be subject to small variations (e.g., due to varying degrees of purity of the ingredients) without departing from the spirit of the invention.

However, the ingredients used for the dermatologic formulations of the invention should be of high quality and purity.

10

The hypoallergenic and non-irritant skin care formulations of the invention are suitable as emollients, for therapy or therapy support of eczematous and psoriatic skin, as well as for therapeutic daily skin care treatment of dry, sensitive skin.

Furthermore, the formulations of the invention may further comprise one or more of the ingredients selected from a sunscreen, a vitamin or vitamin analog, such as Vitamin E, Vitamin K, Calcipotriol, Tacalcitol, or a pharmaceutically active compound, such as corticoids, antimycotics, immunosuppressants, salicylic acid, alpha- or beta-hydroxy acids, or linolenic acid.

The group of corticoids may include but is not limited to hydrocortisone and derivatives thereof, such as methylprednisolone aceponate, diflucortolone valerate, fluocortolone pivalate / hexanoate / monohydrate, fluocortinbutyl, betamethasone and derivatives thereof, clobetasole, triamcinolone acetonide, dexamethasone, prednisolone, and clocortolone pivalate. The group of antimycotics may include but is not limited to ketoconazole, isoconazole, miconazole, and clotrimazole; and the group of immunosuppressants may include but is not limited to ascomycin and derivatives thereof, cyclosporine A, azathioprine, methotrexate, cyclophosphamide, and the like.

The invention furthermore provides a robust and easily applicable method of manufacturing the skin care formulations of the invention. Manufacturing of the skin care formulations is achieved by preparing the oil phase by melting the ingredients of the oil phase such as cetearyl octanoate, dicaprylyl ether, caprylic / capric triglyceride, polyglyceryl-3-diisostearate, polyglyceryl-2-dipolyhydroxystearate, petrolatum, cera alba, and ethylhexylglycerin, with stirring until all ingredients are completely melted. The ingredients chosen for the oil phase will depend on the oil phase that is desired, as described above.

For the water (aqueous) phase, purified water is heated in a separate vessel and the ingredients of the water phase such as magnesium sulfate, sodium lactate, lactic acid, and optionally glycerin, urea, and propylene glycol, are added depending upon the desired composition of the water phase (see above, for example). Such ingredients are dissolved with stirring and subsequently, the pH value of the resulting solution is adjusted with lactic acid to about 4.4 – 4.8. Both the oil and water phase are preferably heated to about 75 – 85°C during melting and dissolution, respectively.

Prior to the combination of the oil and the water phase, the oil phase is filtered through filter cartridges with 0.1 mm filter units for particulate filtration. Subsequently, the emulsion is prepared by transferring the melted oil phase as prepared above to the heated water phase and, while stirring and homogenizing, cooling the emulsion down under vacuum conditions, preferably about -0.6 to -0.9 bar, to room temperature.

Preferably, the oil phase is transferred into the water phase while stirring at about 40 min⁻¹ at 75 - 85°C, cooled down to about 58 - 62°C while stirring and homogenizing at 3000 min⁻¹, further cooled to about 38 - 42°C while stirring and homogenizing at 4000 min⁻¹, and finally cooled down to about 23 - 27°C while stirring. After the cooling process, the prepared semi-solid or semi-liquid W/O emulsions of the present invention can be discharged into appropriate containers.

The invention is further illustrated in the Examples. The Examples are not intended to limit the scope of the invention.

Example 1: Preparation of semi-solid formulation A

A semi-solid formulation according to the invention (designated Formulation A herein below) was prepared in a batch size of 50 kg using an ointment mixer and homogenizer (available under the trade name Becomix® RW 60 from Berents, Germany), equipped with a 60 L stainless steel pan, an infinitely variable anchor-type stirrer, homogenizer and process control system, a pH-meter, a stainless steel melting pan equipped with an infinitely variable stirrer, stainless steel ointment storage containers, and stainless steel sintered filter cartridges, 0.1 mm for particulate filtration.

For the preparation of the water phase, the ointment mixer/homogenizer was charged with 33.7 kg of purified water, 1.5 kg glycerin, 0.5 kg magnesium sulfate, and 0.992 kg sodium lactate and stirred (40 min⁻¹) at 80 ± 2°C until all components were completely dissolved. Subsequently, the pH value was checked and adjusted with 0.058 kg lactic acid to a pH of about 4.6.

The oil phase was prepared by charging the melting vessel with 1.5 kg petrolatum, 1.5 kg cetearyl octanoate, 1.5 kg dicaprylyl ether, 4.0 kg caprylic / capric triglyceride, 1.0 kg cera alba, 2.25 kg polyglyceryl-3-diisostearate, 0.75 kg polyglyceryl-2-dipolyhydroxystearate, and 0.15 kg ethylhexylglycerin and melted completely at 80 ± 2 °C while stirring until no unmelted material remained visible. Finally, the oil phase was filtered through stainless steel filter cartridges with 0.1 mm filter units for particulate filtration prior to the addition to the water phase.

The emulsion was subsequently prepared by transferring the oil phase to the water phase in the ointment mixer/homogenizer with stirring (40 min^{-1}) at 80 ± 2 °C. The resultant mixture was then cooled to 60 ± 2 °C while it was stirred and homogenized (3000 min^{-1} , cycle). The resulting emulsion was then further stirred and homogenized (4000 min^{-1} , cycle) during cooling to 40 ± 2 °C. Finally, stirring of the emulsion was continued until the emulsion had a temperature of 25 ± 2 °C. During the complete cool down process a vacuum of between -0.6 and 0.9 bar was applied.

The resulting cream was checked for homogeneity by microscopy for uniform appearance. After passing the homogeneity test, the product was discharged into bulk containers.

Example 2: Preparation of semi-solid formulation B

Formulation B was prepared as formulation A, with the exception that 4 kg of propylene glycol was added to the water phase and no ethylhexylglycerin was added to the oil phase.

Example 3: Preparation of semi-liquid formulation C

The semi-liquid formulation C was essentially prepared as formulations A and B in Examples 1 and 2. The differences in the manufacturing process are described below.

For the production of formulation C in a batch size of 50 kg, the ointment mixer / homogenizer was charged with 28.35 kg of purified water, 1.5 kg glycerin, 0.5 kg

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magnesium sulfate, 1.867 kg sodium lactate, and 2.5 kg urea and stirred (40 min^{-1}) at $80 \pm 2^\circ\text{C}$ until all components were completely dissolved. Subsequently, the pH value was checked and adjusted with 0.633 kg lactic acid to a pH of about 4.2.

- 5 The oil phase was prepared by charging the melting vessel with 2.5 kg cetearyl octanoate, 1.5 kg dicaprylyl ether, 7.5 kg caprylic/capric triglyceride, 1.0 kg polyglyceryl-3-diisostearate, 2.25 kg polyglyceryl-2-dipolyhydroxystearate, and 0.15 kg ethylhexyl-glycerin and melted completely at $80 \pm 2^\circ\text{C}$ while stirring until no unmelted material remained visible.

10

After particulate filtration, both phases were combined to form an emulsion as described in Example 1. After passing the homogeneity test, the resulting lotion was discharged into bulk containers.

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Example 4: Microbiological/ physicochemical stability

The formulations A, B, and C as prepared in Examples 1 to 3 were subjected to the following stability tests:

- a) Storage at 4°C , 25°C , 30°C , 40°C , 50°C at ambient humidity over 5 months
- 20 b) $-4^\circ\text{C} / 50^\circ\text{C}$ cycle test over 2 weeks
- c) Microbiological challenge test according to USP (United States Pharmacopeia) requirements

25 The formulations were packaged in PE containers (HDPE/LDPE) in batch sizes of 2 – 25 kg and tested for parameters such as pH-value, viscosity (abs.), microscopic and macroscopic picture, content of urea (formulation C), and compatibility with the container material.

30 The test results showed that formulations A – C of Examples 1 – 3 are physicochemically stable under all tested conditions and meet the microbiological stability requirements of the USP.

Example 5: Sensitization and Irritation Risk (HRIPT-Test)

A human repeated insult patch test (HRIPT) was carried out as a 40-days randomized, controlled, double-blind study to assess the sensitizing and irritating potential of the dermatological skin care formulations of the invention. The study was started with 58 healthy volunteers of either sex between 18 and 65 (ITT-cases: n= 58), however, 3 volunteers dropped out and 55 volunteers completed the study (VC-cases: n= 55).

In the induction phase (day 1 – 20), the volunteers were subjected to nine occlusive treatments for 24 hours with 75 µl of the test formulations as prepared in Examples 1 – 3 applied to their backs on days 1, 3, 5, 8, 10, 12, 15, 17, 19. Untreated test fields without application of a test formulation were used as a concurrent control. Skin reactions were evaluated 24 hours (1/2 hour after removal of test chambers; on days 2, 4, 6, 9, 11, 13, 16, 18, 20; nine readings) and 48 hours after the application of occlusive treatments on the backs of the volunteers (1/2 hour after removal of test chambers on days 3, 5, 10, 12, 17, 19; six readings) by a visual 6-point-score.

Visual 6-point-score	
0	Negative/ no reaction
0.5	Equivocal erythema
1	Erythema
2	Erythema and induration (edema)
3	Erythema, induration (edema) and vesicles
4	Erythema, induration (edema) and bullae and/or spreading

The mean cumulative irritation index (M.C.I.I.) was calculated for the 24 hours readings (M.C.I.I./ 24 h.) and for the 48 hours readings (M.C.I.I./ 48 h.).

30

After the treatment-free interval (15 days; days 21-35; no treatment), an occlusive challenge application of the test formulations on yet untreated test sites on the backs of the volunteers was done for 24 hours. The test formulations were evaluated 24 h, 48 h, 72 h and 96 h after the application by the same visual 6-point score (challenge phase; 5 days, days 36-40).

Results:

Sensitization: No case of sensitization occurred in both ITT- and VC-population.

Irritation: No significant irritation potential in comparison to the empty untreated test field could be observed in both ITT- and VC-population.

Furthermore, no adverse events or serious adverse event related to the test formulations was observed during the course of the study.

Example 6: Irritation Potential

The primary objective of this study was to evaluate the cutaneous tolerability of the skin care formulations of the invention over a 4-weeks period when used in the intended way (application twice daily to face or body, respectively) in the intended patient/consumer group having dry and sensitive skin. The secondary objectives of this study were to evaluate the irritation potential of the test formulations A and B when used around the eyes, to evaluate the hydrating effect of all test formulations as measured by corneometry, to evaluate the volunteer's general cosmetic acceptance of all test formulations, and finally to evaluate the cosmetic acceptance of the test formulations A and B as make-up foundations.

The study was designed as a single center, randomized study; double-blinded with interindividual comparison of treatments between the test formulations A, B, and comparative commercially available products for facial application and between test formulation C and comparative commercially available products for body application, and was performed for 28 consecutive days.

Healthy volunteers of either sex between 18 and 65 years old meeting specific inclusion/exclusion criteria with dry skin proven by low corneometer values (≤ 70) were chosen for this study. In addition, 50% of the volunteers were healthy individuals with atopic diathesis according to the atopy score of Diepgen without history for atopic dermatitis. The other 50% of the volunteers were without atopic diathesis. All volunteers in all treatment groups treated face and body twice daily at home over 28 consecutive days with the respective test formulations.

For the measurement of the hydrating effects of the test formulations for facial application, corneometry of both cheek bones was performed on days 1 and 29. For the test formulation for body application, corneometry of both anterior lower legs was performed on screen and on days 1 and 29.

A clinical assessment was performed at screen and on days 1, 8, 15 and 29 using a visual 5-point score (no / doubtful / slight / moderate / severe signs of irritation, erythema and/or scaling). Out of the results of the visual 5-point score an irritation product profile was created with four irritation groups being the primary variable of this study. Subjective symptoms were asked on days 8, 15 and 29 using a 5-point score for subjective evaluation (no / doubtful / slight / moderate / severe sensation of stinging / burning / pruritus with specification in case of any positive answer). Additionally, an ophthalmological examination investigating fore- and background of the eyes as well as the conjunctival mucosa and subjective ophthalmological symptoms using a 5-point score for subjective ophthalmological symptoms took place on days 1 and 29.

Additionally, a questionnaire concerning the sensorial profile and overall cosmetic acceptance (parameters: distribution/spreading, absorption, feeling on the skin, stickiness, greasiness, oily shine, odor, and color; evaluation on a 5-point scale) was filled in by the volunteers on day 29.

Results:

Table 1 summarizes the hydration effect as measured by corneometry of three embodiments of the invention (formulations A, B and C) in comparison to a reference product.

Table 1: Measurement of Hydration Effect by Corneometry

Hydration effect (Corneometry)	Hydration improvement on Day 29 (in %) subgroup I (atopic subjects)	Hydration improvement on Day 29 (in %) subgroup II (non-atopic subjects)	Hydration improvement on Day 29 (in %) subgroup I + II
Formulation A (cream)	43.1	21.0	32.1
Formulation B (cream)	31.2	39.1	35.1
Formulation C (milk)	38.6	45.7	42.2
Reference product [§]	37.1	22.2	29.7

measured by corneometry of both cheek bones (Formulations A and B) and both anterior lower legs (Formulation C), respectively.

[§] commercially available W/O emulsion

In sum, application of the test formulations A, B and C for 28 days resulted in a significant hydration improvement between 32 % and 42 %, averaged over both subgroups (atopic and non-atopic subjects).

The results of the cutaneous tolerability study of formulations A, B, and C are summarized in Table 2. Tables 2 (a) and (b) show the results of the dermatological and ophthalmological investigations, respectively.

Table 2: Results of Tolerability Study (Irritation Potential)**Table 2 (a): Dermatological Investigation:**

Dermatological Investigation (ITT)	Face Formulations		Body Formulation
	Formulation A	Formulation B	Formulation C
(1) Irritation profile: objective signs	1/20 patients: moderate irritation and stop of treatment on day 14	1/20 patients: slight irritation; reduction of treatment dose	-
(2) Partial or transient stop of treatment related or possibly related to test formulation			-
Objective signs of irritation: (1) + (2)	5%	5%	-
(3) Irritation profile, subjective symptoms	1/20 patients: slight pruritus	2/20 patients: slight stinging 1/20 patients: slight pruritus	2/19 patients: slight stinging
Subjective signs of irritation: (3) moderate or severe reactions	-	-	-
Mean Sum of irritation score	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00
Conclusion	Very good irritation profile	Excellent irritation profile	Excellent irritation profile

Table 2 (b): Ophthalmological Investigation

Ophthalmological Investigation	Face Formulations		Body Formulation
	Formulation A	Formulation B	Formulation C
<i>Ophthalmologic objective symptoms</i>	1/20 patients: moderate conjunctival allergy left eye and mild conjunctival allergy right eye*	-	<i>body formulation not tested around the eyes</i>
<i>Ophthalmologic subjective symptoms</i>	1/20 patients: moderate subjective symptoms*	1/20 patients: slight itching tearing of left eye*	
<i>Application interrupted or stopped due to ophthalmological symptoms</i>	-	-	
Conclusion	Excellent tolerability of formulations when applied around the eyes		

* Subsequent studies demonstrated that the above symptoms were not caused by Formulations A and B.

As evident from the tabulated results, all tested dermatologic formulations of the invention exhibited a very good or even excellent irritation profile.

Additionally, the results of the questionnaire concerning the cosmetic acceptance of formulations A, B, and C are depicted in Tables 3 (a) –(i). The following parameters were tested: overall cosmetic quality (Table 3(a)); distribution / spreading (Table 3(b)); absorption (Table 3(c)); feeling on the skin (Table 3(d)); stickiness (Table 3(e)); greasiness (Table 3(f)); oily shine (Table 3(g)); odor (Table 3 (h)); color (Table 3 (i)).

Table 3: Results of sensory assessment tests

All values are given in % of volunteers.

Table 3 (a): Overall opinion of the cosmetic qualities of formulations A - C

Overall opinion	excellent	very good	good	acceptable	bad	no comment
Formulation A (cream)	16	42	32	5	5	0
Formulation B (cream)	15	10	45	5	10	15
Formulation C (lotion)	26	16	37	5	11	5

Table 3 (b): Distribution / Spreading

Distribution / Spreading	very easy	easy	moderately easy	difficult	very difficult
Formulation A (cream)	16	26	26	5	26
Formulation B (cream)	30	0	30	20	20
Formulation C (lotion)	11	5	16	11	58

5 Table 3 (c): Absorption

Absorption	very quick	quick	quite quick	slowly	very slowly	no comment
Formulation A (cream)	26	11	26	11	26	0
Formulation B (cream)	30	15	10	15	25	5
Formulation C (lotion)	21	0	11	21	47	0

Table 3 (d): Feeling on the skin

Feeling on the skin	too light	light	just right	heavy	too heavy
Formulation A (cream)	11	5	26	21	37
Formulation B (cream)	10	5	30	25	30
Formulation C (lotion)	5	5	11	21	58

Table 3 (e): Stickiness

Stickiness	not at all sticky	very few sticky	somewhat sticky	quite sticky	sticky
Formulation A (cream)	26	5	37	11	21
Formulation B (cream)	15	10	45	15	15
Formulation C (lotion)	0	0	26	32	42

Table 3 (f): Greasiness

Greasiness	not at all greasy	very few greasy	somewhat greasy	quite greasy	greasy
Formulation A (cream)	11	5	32	42	11
Formulation B (cream)	15	0	20	55	10
Formulation C (lotion)	5	5	26	63	0

5 Table 3 (g): Oily shine

Oily shine	leaves no oily shine	leaves a very light oily shine	leaves a light oily shine	leaves an oily shine	leaves a very oily shine	No comment
Formulation A (cream)	21	5	21	37	16	
Formulation B (cream)	15	0	25	20	40	
Formulation C (lotion)	16	0	11	37	32	5

Table 3 (h): Odor

Odor	no	yes, very light	yes, light	yes, moderate	yes, strong	yes, very strong
Formulation A (cream)	53	16	21	0	5	5
Formulation B (cream)	40	35	15	5	5	0

Formulation C (lotion)	58	21	16	5	0	0
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Table 3 (i): Color

Color	very pleasant	pleasant	unpleasant	I don't care	no comment
Formulation A (cream)	16	53	16	16	0
Formulation B (cream)	20	45	15	20	0
Formulation C (lotion)	16	53	26	5	0

5 **Example 7: Phototoxicity**

In order to assess the phototoxic potential of the dermatologic skin care formulations of the invention, the semi-solid formulations of example 1 and 2 were tested in a phototoxicity study running for 5 consecutive days. The study was designed as a single center, randomized, double-blind study with intraindividual comparison of treatments and inter-individual comparison of treatments for the test formulations A and B. 12 healthy volunteers of either sex between 18 and 50 years old meeting specific inclusion/ exclusion criteria were enrolled in the study. 50 μ l of each test formulation was applied under occlusive conditions in duplicate on subject's back on days 1 for 24 hours. One duplicate test field without application of a formulations (empty test chamber with/without UV-radiation) was used as a control.

On day 1 and 2, the minimal erythema dose (MED) was assessed by irradiation of six small test fields with UVA/B on the upper back of the volunteer. The test chambers with the test formulations in duplicate were applied on day 1 to the designated test fields on both sides of the mid back of the volunteers. On day 2, the test chambers were removed after 24 hours and the test fields (20 J/cm^2 UVA + $0.75 \times \text{MED}$ UVA+UVB) were irradiated on the left side of the mid back. The skin reactions were evaluated after one hour (day 2), after 24 hours (day 3), after 48 hours (day 4) and after 72 hours (day 5) using a 5-point visual score:

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Visual 5-point score	
0	No erythema
0.5	Equivocal erythema (barely perceptible erythema with no clearly defined border)
1	Mild but definite erythema with clearly defined border (MED)
2	Moderate, clearly defined erythema
3	Severe erythema, with or without infiltration
4	Severe erythema with vesicles or bullous reaction

The number of volunteers who experienced a phototoxic reaction during the study determined the phototoxic potential of the test formulations.

- 5 **Results:** No case of phototoxicity could be observed with the dermatologic formulations A and B during the study in the test population.

Example 8: Photo-Sensitization Risk

- 10 The primary objective of this study was to evaluate the photosensitizing potential of the dermatologic formulations of the invention in a population of n=25 healthy volunteers of either sex between 18 and 65 years with Fitzpatrick's skin type I, II, or III meeting specific inclusion/ exclusion criteria using the modified method of Kaidbey & Kligman (Kaidbey & Kligman, 1980, *Contact Dermatitis* 6, 161-169). The secondary objective of this study was to evaluate the sensitization potential of the formulations.

- 20 The study was designed as a single center, randomized, double-blind study with intraindividual comparison of treatments and interindividual comparison of treatments for the test formulations including formulations A and B (cream) and was performed for 6 consecutive weeks. As a control, untreated test fields without application of test formulations were included into the study.

During the induction phase one series of test plasters with all test formulations and one empty field was fixed on the left sides of the backs. During the challenge phase two series of test plasters were fixed on each side of the back. Only the right side of the back was irradiated. Allocation of test formulations to test fields was identical for each volunteer
5 during induction and challenge phase. For each application, 50 µl of the test formulation was applied under occlusive conditions on volunteers' backs on days 1, 4, 8, 11, 15, 18, and 36.

10 The MED of each subject was determined by irradiating increasing doses of UVA/UVB/ with a solar simulator on previously selected sites of the volunteers back. Scoring was performed 24 hours after the irradiation. The MED is the smallest dose (mJ/cm²) needed to induce a visible, clearly delineated erythema.

15 In the induction phase (20 days; day 1-20), six occlusive applications of one series of test formulations were done for 24 hours on the left side of the backs of volunteers on days 1, 4, 8, 11, 15, 18. After 24 h, the occlusive treatments were removed and all test fields were consecutively exposed to 3 x MED UVA/UVB with a solar simulator on days 2, 5, 9, 12, 16, and 19. The results were evaluated 24 h after the irradiation by a 6-point visual score.

20 In the challenge phase (5 days; day 36-40) after the treatment-free interval (15 days; day 21-35), occlusive application of two series of test formulations on yet untreated sites on both sides of the backs of the volunteers were performed for 24 hours (challenge application). Consecutively, the test fields were exposed on the right side of the backs to 10 J/cm² UVA plus 0.75 x MED (UVA/UVB) (challenge irradiation on day 37). The
25 results were evaluated one hour after the challenge irradiation and additionally 24 h, 48 h and 72 h after challenge irradiation by a 6-point visual score.

The following 6-point visual score was used during induction and challenge phase:

Visual 6-point-score	
0	No erythema
0.5	Equivocal erythema
1	Definite erythema with clearly defined border (MED)
2	Erythema with infiltration/ papules
3	Erythema with vesicles or bullous reaction
4	Erythema with eroded bullous reaction and/or raised spreading reaction beyond the borders of the patch site

Results: No case of photosensitization could be observed under the above-described conditions for the dermatological formulations A and B of Example 1 and 2 (facial formulations) in any of the volunteers.

Claims:

1. A hypoallergenic and non-irritant skin care formulation, wherein the formulation:
 - a) is free from fragrances, preservatives, colorings, plant extracts, PEGs, cetylstearyl alcohol, lanolin alcohol, lower alcohols and proteins; and
 - 5 b) comprises a water phase dispersed in an oil phase, wherein the oil phase comprises cetearyl octanoate, dicaprylyl ether, caprylic / capric triglyceride, polyglyceryl-3-diisostearate and polyglyceryl-2-dipolyhydroxystearate.
- 10 2. The skin care formulation according to claim 1, the formulation having a total number of ingredients that is less than 15.
3. The skin care formulation according to claims 1 – 2, wherein the water phase comprises the ingredients purified water, magnesium sulfate, lactic acid and sodium lactate.
- 15 4. The skin care formulation according to claims 1 – 3, wherein the water phase further comprises glycerin.
- 20 5. The skin care formulation according to claims 1 – 4, wherein the oil phase further comprises ethylhexylglycerin.
6. The skin care formulation according to claims 1 – 4, wherein the oil phase of the formulation further comprises petrolatum and cera alba.
- 25 7. The skin care formulation according to claim 6, wherein the oil phase further comprises ethylhexylglycerin.
8. The skin care formulation according to claim 6, wherein the water phase further comprises propylene glycol.

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9. The skin care formulation according to claims 1 - 5, wherein the water phase further comprises urea.

5 10. A semi-solid skin care formulation comprising the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

	a) petrolatum:	2 - 5 %
	b) cetearyl octanoate:	2 - 5 %
0	c) dicaprylyl ether:	1 - 3 %
	d) caprylic / capric triglyceride:	5 - 10 %
	e) cera alba:	1.0 - 2.5 %
	f) polyglyceryl-3-diisostearate:	4 - 5 %
	g) polyglyceryl-2-dipolyhydroxystearate:	1 - 2 %
15	h) ethylhexylglycerin:	0 - 0.8 %

(2) water phase:

	a) glycerin:	0 - 5 %
	b) magnesium sulfate:	0.5 - 1.5 %
20	c) lactic acid :	0.05 - 1.5 %
	d) sodium lactate:	1 - 5 %
	e) purified water:	add to 100 %

25 11. A semi-solid skin care formulation, wherein the formulation comprises the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

	a) petrolatum:	2 - 5 %
	b) cetearyl octanoate:	2 - 5 %
30	c) dicaprylyl ether:	1 - 3 %

- d) caprylic / capric triglyceride: 5 – 10 %
- e) cera alba: 1.0 – 2.5 %
- f) polyglyceryl-3-diisostearate: 4 – 5 %
- g) polyglyceryl-2-dipolyhydroxystearate: 1 – 2 %

5

(2) water phase:

- a) glycerin: 0 – 5 %
- b) magnesium sulfate: 0.5 – 1.5 %
- c) lactic acid : 0.05 – 1.5 %
- d) sodium lactate: 1 – 5 %
- e) propylene glycol: 5 – 10 %
- f) purified water: add to 100 %

10

- 15 12. A semi-liquid skin care formulation comprising the following ingredients expressed as a percent by weight (% w/w) range:

(1) oil phase:

- a) cetearyl octanoate: 2 – 5 %
- b) dicaprylyl ether: 1 – 3 %
- c) caprylic / capric triglyceride: 8 – 15 %
- d) polyglyceryl-3-diisostearate: 1.5 – 3 %
- e) polyglyceryl-2-dipolyhydroxystearate: 3 – 5 %
- f) ethylhexylglycerin: 0 – 0.8 %

20

(2) water phase:

- a) glycerin: 0 – 5 %
- b) magnesium sulfate: 0.5 – 1.5 %
- c) lactic acid : 0.05 – 1.5 %
- d) sodium lactate: 1 – 5 %
- e) urea: 0.5 – 10 %
- f) purified water: add to 100 %

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3X

13. The skin care formulation according to any of claims 1 – 12, wherein the formulation further comprises one or more pharmaceutically active compounds, vitamins or vitamin analogs, and/or sunscreens.

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14. The skin care formulation according to claim 13, wherein the pharmaceutically active compound is a corticoid, an antimycotic, salicylic acid, an alpha- or beta-hydroxy acid, and/or linolenic acid; wherein the vitamin is Vitamin E, or Vitamin K; and wherein the vitamin analog is Calcipotriol, or Tacalcitol.

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15. The skin care formulation according to any of claims 1 – 14 for use in the prophylaxis and treatment of dry, sensitive skin or the therapy of eczematous skin and psoriatic skin.

- 15 16. A method of manufacturing a hypoallergenic and non-irritant skin care formulation comprising the steps of:

- a) preparing an oil phase by melting the ingredients of the oil phase as defined in any one of claims 1, 5, 6, 7, or 10 – 12;
- 20 b) preparing a water phase by heating purified water and dissolving therein the ingredients of the water phase as defined in any of claims 3, 4, 8, or 10 – 12 while stirring and adjusting the pH value of the resulting solution with lactic acid to about 4.4 – 4.8;
- 25 c) preparing a water-in-oil emulsion by transferring the melted oil phase from step (a) to the heated water phase of step (b) and, while stirring and homogenizing, cooling the emulsion down to room temperature while applying a vacuum of about -0.6 to -0.9 bar.

- 30 17. The method of claim 16, wherein step (a) and step (b) are performed at a temperature of about 75 – 85°C and wherein step (c) comprises the steps of transferring the oil phase of step (a) into the water phase of step (b) while stirring at

about 40 min⁻¹ at 75 – 85°C, cooling the emulsion down to about 58 – 62°C while stirring and homogenizing at 3000 min⁻¹, cooling the emulsion further down to about 38 – 42°C while stirring and homogenizing at 4000 min⁻¹, cooling the emulsion further down to about 23 – 27°C while stirring, and discharging the emulsion into appropriate containers.

PCT REQUEST

Original (for SUBMISSION) - printed on 13.12.2001 04:20:41 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	SCH10130PCT
I	Title of invention	HYPOALLERGENIC AND NON-IRRITANT SKIN CARE FORMULATIONS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	Schering AG
II-5	Address:	Müllerstrasse 178 D-13353 Berlin Germany
II-6	State of nationality	DE
II-7	State of residence	DE
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	Franke, Patrick
III-1-5	Address:	McNair-Promenade 124 D-14167 Berlin Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN
IV-1-2	Address:	Triftstr. 13 D-80538 München Germany
IV-1-3	Telephone No.	089/2102960
IV-1-4	Facsimile No.	089/21029633
IV-1-5	e-mail	info@df-mp.com
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	15 December 2000 (15.12.2000)
VI-1-2	Number	00127555.1
VI-1-3	Regional Office	EP
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	15 December 2000 (15.12.2000)
VI-2-2	Number	60/255,379
VI-2-3	Country	US

VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	1	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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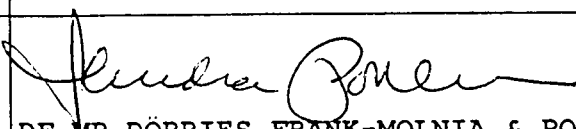
SCH10130PCT

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VIII-1-1	Declaration: Identity of the Inventor	
	Declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i))	in relation to this international application
	Name: Address:	Franke, Patrick of McNair-Promenade 124 D-14167 Berlin Germany is the inventor of the subject matter for which protection is sought by way of this international application
	This declaration is made for the purposes of:	all designations

PCT REQUEST

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	25	-
IX-3	Claims	5	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	36	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. 42894	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
	Signature of applicant, agent or common representative		
X-1-1	Name	DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN	
X-1-2	Name of signatory	Sandra Pohlman	
X-1-3	Capacity	Solicitor (England & Wales), Legal Practitioner No. 157080	

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/14825

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 198 43 876 A (COGNIS DEUTSCHLAND GMBH) 13 April 2000 (2000-04-13) table 1	1-17
A	EP 0 847 750 A (BEIERSDORF AG) 17 June 1998 (1998-06-17) examples 1-16	1-17
A	ANOM.: "Final Report on the safety assessment of Cetearyl Octanoate" J. AMERICAN COLLEGE OF TOXICOLOGY, vol. 1, no. 4, 1982, pages 81-90, XP000982324 the whole document	1-17

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document 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.

8 document member of the same patent family

Date of the actual completion of the international search

8 April 2002

Date of mailing of the international search report

16/04/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Sierra Gonzalez, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14825

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 19843876	A	13-04-2000	DE 19843876 A1	13-04-2000
			AU 6084499 A	17-04-2000
			WO 0018357 A1	06-04-2000
			EP 1115365 A1	18-07-2001
EP 0847750	A	17-06-1998	DE 19651478 A1	18-06-1998
			EP 0847750 A2	17-06-1998
			JP 10175839 A	30-06-1998

PATENT COOPERATION TREATY

44

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

DF-MP DÖRRIES FRANK-MOLNIA &
POHLMAN
Triftstr. 13
D-80538 München
ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 19/08/2002

Applicant's or agent's file reference

SCH10130PCT

IMPORTANT NOTIFICATION

International application No.

PCT/EP 01/ 14825

International filing date (day/month/year)

14/12/2001

Priority date (day/month/year)

15/12/2000

Applicant

SCHERING AG

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27 (5), 33 (5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/

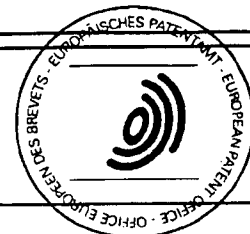


European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

CARDENAS C E

Tel. (+49-89) 2399 2828



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCH10130PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 01/ 14825	International filing date (day/month/year) 14/12/2001	Priority date (day/month/year) 15/12/2000
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant SCHERING AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 03/07/2002	Date of completion of this report 13/08/2002
Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+ 31-70) 340-2040 Fax: (+ 31-70) 340-3016	Authorized officer FLETCHER A S Tel. (+ 49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/ EP 01/ 14825

46.

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

PCT/EP01/14825

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:	Deadline:
DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN Triftstr. 13 80538 München Germany	RECEIVED 05. Juni 2003 df-mp Dörries, Frank-Molnia & Pohlman Patents - Trademarks - Designs

Date of mailing (day/month/year) 21 May 2003 (21.05.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SCH10130PCT	
International application No. PCT/EP01/14825	International filing date (day/month/year) 14 December 2001 (14.12.01)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address SCHERING AG Müllerstrasse 178 13353 Berlin Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address FRANKE, Patrick McNair-Promenade 124 14167 Berlin Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Please note that the applicant in box I has assigned their rights to the applicant in box II. The latter is now applicant/inventor for all designated states.

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Alison OSBORNE (Fax : 338 89 75)
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338 8472

PCT REQUEST

Original (for SUBMISSION) - printed on 13.12.2001 04:20:41 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	SCH10130PCT
I	Title of invention	HYPOALLERGENIC AND NON-IRRITANT SKIN CARE FORMULATIONS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	Schering AG
II-5	Address:	Müllerstrasse 178 D-13353 Berlin Germany
II-6	State of nationality	DE
II-7	State of residence	DE
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	Franke, Patrick
III-1-5	Address:	McNair-Promenade 124 D-14167 Berlin Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

SCH10130PCT

Original (for SUBMISSION) - printed on 13.12.2001 04:20:41 PM

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN
IV-1-2	Address:	Triftstr. 13 D-80538 München Germany
IV-1-3	Telephone No.	089/2102960
IV-1-4	Facsimile No.	089/21029633
IV-1-5	e-mail	info@df-mp.com
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	15 December 2000 (15.12.2000)
VI-1-2	Number	00127555.1
VI-1-3	Regional Office	EP
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	15 December 2000 (15.12.2000)
VI-2-2	Number	60/255,379
VI-2-3	Country	US

PCT REQUEST

SCH10130PCT

Original (for SUBMISSION) - printed on 13.12.2001 04:20:41 PM

VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	1	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

PCT REQUEST

SCH10130PCT

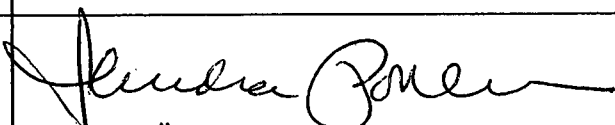
Original (for SUBMISSION) - printed on 13.12.2001 04:55:14 PM

VIII-1-1	Declaration: Identity of the Inventor Declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i))	in relation to this international application
	Name: Address:	Franke, Patrick of McNair-Promenade 124 D-14167 Berlin Germany is the inventor of the subject matter for which protection is sought by way of this international application
	This declaration is made for the purposes of:	all designations

PCT REQUEST

SCH10130PCT

Original (for SUBMISSION) - printed on 13.12.2001 04:20:41 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	25	-
IX-3	Claims	5	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	36	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. 42894	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN	
X-1-2	Name of signatory	Sandra Pohlman	
X-1-3	Capacity	Solicitor (England & Wales), Legal Practitioner No. 157080	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:	Deadline:
DF-MP DÖRRIES, FRANK-MOLNIA & POHLMAN Triftstr. 13 D-80538 München 21. Aug. 2002 ALLEMAGNE df-mp Dörries, Frank-Molnia & Pohlman Patents · Trademarks · Designs	
Reminder:	

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) **19/08/2002**

Applicant's or agent's file reference
SCH10130PCT

IMPORTANT NOTIFICATION

International application No. PCT/EP 01/ 14825	International filing date (day/month/year) 14/12/2001	Priority date (day/month/year) 15/12/2000
--	---	---

Applicant

SCHERING AG

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
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Name and mailing address of the IPEA/

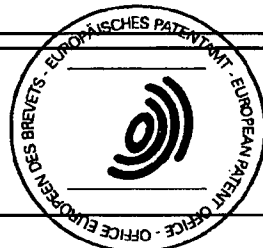


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Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCH10130PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 01/ 14825	International filing date (day/month/year) 14/12/2001	Priority date (day/month/year) 15/12/2000
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant SCHERING AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03/07/2002	Date of completion of this report 13/08/2002
Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer FLETCHER A S Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/ EP 01/ 14825



I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.



patents • trademarks • designs

Dörries
Frank-Molnia
& Pohlman

Mail Postfach 22 16 61, D - 80506 München • Visitors Triftstrasse 13, D - 80538 München

Phone +49 89 210296 0 • Fax +49 89 210296 33 • info@df-mp.com • www.df-mp.com

European Patent Office
Erhardtstrasse 27
80331 Munich

December 6, 2002

Official Ref.: PCT/EP01/14825
Title: Hypoallergenic and Non-Irritant Skin Care Formulations
Applicant: Dr. Patrick Franke (privat)
Our Ref.: SCH10130PCT

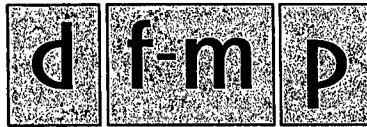
Further to our letter of August 26, 2002, please be informed that the address of the applicant/inventor **Dr. Patrick FRANKE** has changed.

We respectfully request that the correct information be recorded in the European Patent Register as follows:

Dr. Patrick FRANKE
McNair-Promenade 124
14167 Berlin
DEUTSCHLAND

Respectfully,

David Molnia
European Patent Attorney



patents • trademarks • designs

Dörries
Frank-Molnia
& Pohlman

Mail Postfach 22 16 61, D - 80506 München • Visitors Triftstrasse 13, D - 80538 München
Phone +49 89 210296 0 • Fax +49 89 210296 33 • info@df-mp.com • www.df-mp.com

European Patent Office

80298 Munich

August 26, 2002

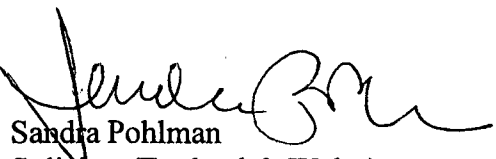
Official Ref.: PCT/EP01/14825
Title: Hypoallergenic and Non-Irritant Skin Care Formulations
Previous Applicant: Schering AG
New Applicant: Dr. Patrick Franke
Our Ref.: SCH10130PCT

We herewith request the registration of the transfer of the above-mentioned International Application from the applicant Schering AG to the inventor

Dr. Patrick FRANKE.

The address of the inventor has changed. We respectfully request that the new information be recorded as follows:

Dr. Patrick FRANKE
Ringbahnstraße 7
10711 Berlin
DEUTSCHLAND


Sandra Pohlman
Solicitor (England & Wales)
Legal Practitioner No. 157080

SP/KS

H. Ulrich Dörries • Dr. Sc. Nat., Dipl.-Biol., Patentanwalt, European Patent & Trademark Attorney
David Molnia • M.S. Elec. Eng., Patentanwalt, European Patent & Trademark Attorney, U.S. Patent Agent
Sandra Pohlman • B.S. Biology, U.S. Patent Attorney, Solicitor (England & Wales)

91.237
2

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19) ORGANIZACION MUNDIAL DE LA PROPIEDAD INTELECTUAL
Oficina Internacional



(43) Fecha de Publicación Internacional:
20 de junio del 2002 (20.06.2002)

(10) Número de Publicación Internacional:
WO 02/47642 A1

PCT

(51) Clasificación de Patente Internacional⁷: **A61K 7/48**

(21) Número de Solicitud Internacional: PCT/EP01/14825

(22) Fecha de Presentación Internacional:
14 de diciembre del 2001 (14.12.2001)

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos de Prioridad:
00127555.1 15 de diciembre del 2000 (15.12.2000) EP
60/255,379 15 de diciembre del 2000 (15.12.2000) US

(84) Estados Designados (*regional*): patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Solicitante (para todos los Estados designados excepto US): SCHERING AG [DE/DE]; Müllerstrasse 178, 13353 Berlin (DE).

Declaración bajo la Regla 4.17

— en cuanto a la identidad del inventor (Regla 4.17(ii)) para las siguientes designaciones

(72) Inventor: Y

(75) Inventor/Solicitante (*para EU únicamente*): **FRANKE, Patrick** [DE/DE]; McNair-Promenade 124, 14167 Berlin (DE).

(74) Agente: **DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN**; Triftstr. 13, 80538 München (DE).

Publicada

- Con el informe de búsqueda internacional.
- Antes de que termine el tiempo límite para enmendar las reivindicaciones para ser republicada en el caso del recibo de enmiendas.

(81) Estados Designados (*nacional*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

Para los códigos de dos letras, y otras abreviaciones, referidas en la "Guide-ance Notes on Codes and Abbreviations" aparecen al comienzo de cada edición regular de la Gaceta PCT



WO 02/47642 A1

(54) Título: FORMULACIONES PARA EL CUIDADO DE LA PIEL HIPOALERGÉNICAS Y NO IRRITANTES

(57) Resumen:

La invención proporciona formulaciones médicas para el cuidado de la piel hipoalergénicas y no irritantes novedosas siendo emulsiones de agua en aceite. Las formulaciones no tienen ingredientes con potencial alergénico conocido, tal como fragancias, conservadores, colorantes, extractos vegetales, Los PEG, alcohol cetil estearílico, alcohol lanolínico, alcoholes bajos y proteínas, de este modo siendo particularmente adecuados para pacientes con piel seca sensible. Las formulaciones para el cuidado de la piel de la invención son útiles en la profilaxis y tratamiento de la piel sensible seca o la terapia o apoyo de terapia de la piel eczematosa o psoriática y muestran propiedades sensoriales favorables. La invención además proporciona un método para fabricar las formulaciones para el cuidado de la piel hipoalergénicas y no irritantes novedosas.

57

FORMULACIONES PARA EL CUIDADO DE LA PIEL HIPOALERGÉNICAS Y NO IRRITANTES

Campo de la Invención

5 Esta invención está relacionada con formulaciones para el cuidado de la piel hipoalergénicas y no irritantes. Las formulaciones de la invención son particularmente adecuadas para aplicaciones médicas tal como para tratar piel seca, piel sensible y para terapia de condiciones de la piel tal como
10 eczema y psoriasis. Las formulaciones de la invención son benéficas y superiores a las formulaciones previamente conocidas que reclaman ser hipoalergénicas y no irritantes.

Antecedentes de la Invención

15 La piel humana actúa como una barrera y capa protectora contra las inclemencias químicas, físicas y mecánicas. La función principal de la capa exterior de la piel—la capa callosa— es para evitar la pérdida de agua y sustancias vitales hacia el ambiente mientras que evita que
20 materiales exógenos nocivos entren al tejido vivo. Las personas expertas en la técnica hacen referencia a la capa callosa exterior tal como *stratum corneum* (SC). Otras funciones de la SC incluyen la regulación de los mecanismos homeostáticos para asegurar las condiciones de estado uniforme de frente a un
25 ambiente cambiante, mecanismos de reparación después de afectar

la barrera por enfermedad o inclemencias exógenas y la presencia de sustancias antibacterianas para proteger contra la infección. Para poder cumplir con estas funciones, la SC necesita estar hidratada y ser flexible.

5 Los mecanismos complicados en la piel mantienen el estado de hidratación esencial de la SC. Sin embargo, muchos factores funcionan para comprometer a la barrera SC e incrementar la velocidad de pérdida de agua. La exposición a condiciones severas, incluyendo el frío, el clima de invierno
10 seco, lavado frecuente con jabón y agua caliente, exposición a agentes tensioactivos, productos químicos irritantes o solventes pueden provocar la sequedad de la piel. Además de los factores externos que provocan las condiciones de piel seca, se conocen varias enfermedades que están caracterizadas por una
15 condición o comportamiento anormal de la SC. Ejemplos de estas enfermedades son dermatitis atópica, psoriasis e ictiosis.

La SC muda grupos de células conocidos tal como corneocitos de la superficie de la piel mientras que se reponen continuamente desde de las capas subyacentes. Este proceso
20 usualmente es imperceptible debido al pequeño tamaño de los grupos, pero la piel seca, los agregados más grande de estas células se mudan en forma de escamas u hojuelas. La piel seca está caracterizada por una sensación seca áspera y una apariencia escamosa. Puede provocar comezón y tornarse roja e
25 irritada, y las personas que sufren de piel muy seca (sequedad

excesiva) pueden rasarse las áreas afectada de manera repetida. Si tales condiciones no se tratan, la piel severamente seca puede resquebrajarse y sangrar. La acumulación de escamas quebradizas gruesas puede ocurrir tal como en la psoriasis y varias formas de ictiosis.

Los humectantes de piel se utilizan para ayudar a prevenir que la piel se seque o para devolverle a la piel seca su condición normal. Se conocen varios compuestos que actúan como hidratantes o humectantes de piel. Entre estos están el glicerol (glicerina), urea, petrolato (vaselina), glicoles de polietileno (los PEG), lanolinas (ceras de lana), ácido láctico (lactato), y ceramidas. En los productos del cuidado de la piel, estos ingredientes se formulan junto con una gran variedad de otros ingredientes utilizados para maximizar la eficacia, la estabilidad y la vida de anaquel. Para los productos del cuidado de la piel, las impresiones subjetivas del usuario son particularmente importantes. De este modo, los ingredientes para mejorar las propiedades subjetivas tal como pegajosidad/adiposidad, distribución/propagación, absorción, olor, o color también se adicionan. Típicamente, los productos del cuidado de la piel están compuestos de aproximadamente 20-50 ingredientes diferentes, ya que es la experiencia de la persona experta en la técnica que resultados favorables pueden no lograrse por formulaciones con menos ingredientes.

Los ingredientes de las formulaciones del cuidado de

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la piel generalmente se combinan para formar una emulsión, ya que consisten de ingredientes hidrofóbicos e hidrofílicos. En principio, dos tipos básicos de emulsiones son posibles. En una emulsión de aceite en agua (O/W), la fase de aceite forma la fase discontinua, mientras que la emulsión de agua en aceite (W/O), la fase de agua representa la fase discontinua.

La mayoría de los productos y el cuidado de la piel están formulados tal como emulsiones O/W. Las emulsiones O/W usualmente son preferidas para cosméticos, debido a sus propiedades cosméticas favorables que son agradables para los consumidores. Una emulsión O/W sin embargo, representa un efecto desfavorable de tales propiedades agradables para el usuario, ya que las emulsiones O/W generalmente son menos efectivas que las emulsiones W/O para tratar o mejorar las condiciones de la piel seca.

Se ha sugerido que las emulsiones W/O son adecuadas tal como una terapia adjunta en el tratamiento de psoriasis, de este modo proporcionando un efecto escaso en esteroides (Watsky et al., 1992, *Cutis* 50, 1992). En la Patente Norteamericana No. 5,561,166, Sattler et al., describe una composición W/O que contiene urea y sales de ácido láctico para el tratamiento de la piel seca. Adicionalmente, la Patente Norteamericana No. 5,552,147 describe composiciones cosméticas que contienen ácidos alfa hidroxí carboxílicos dispersos en vaselina con la ayuda de un fosfátido.

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Un problema común asociado con los productos del cuidado de la piel es que provocan efectos adversos en consumidores o pacientes. Tales efectos no deseados incluyen irritación (subjetiva y objetiva), dermatitis de contacto alérgico, dermatitis de fotocontacto, y reacciones de contacto inmediato (*"Dry Skin and Moisturizers: Chemistry & Function"* p. 403, Eds. Loden & Maibach, 2000). En este contexto, se deberá entender que las reacciones irritantes son distintas a las reacciones alérgicas debido a sus diferentes características y/o modo de acción. Las técnicas establecidas tal como pruebas por parches son conocidas por aquellos expertos en la técnica y pueden utilizarse para diferenciar entre los dos tipos de reacción (véase por ejemplo, *"Unwanted effects of cosmetics and drugs used in dermatology"*, pp. 6-10, Eds. De Groot, Weyland and Nater, Elsevier 1994).

El efecto secundario más frecuentemente observado es la dermatitis de contacto alérgico. Esta reacción usualmente es causada por fragancias y conservadores presentes en estos productos. Otro origen de las reacciones alérgicas es el humectante tal como lanolina y sus derivados, emulsificantes tal como cocamidopropil betaina, y emolientes.

Aunque muchos de los ingredientes típicamente utilizados en las formulaciones del cuidado de la piel tienen un potencial de sensibilización de irritación no alérgico conocido y el índice de reacciones alérgicas en los

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consumidores o pacientes ha incrementado dramáticamente los últimos años, estos ingredientes aún se utilizan en la mayoría de los productos en el mercado del cuidado de la piel hoy en día. Varias formulaciones del cuidado de la piel reclaman tener bajo contenido de ciertos alergen^{os} y/o irritantes. La Patente Norteamericana No. 5,863,546 describe composiciones cosméticas, que difieren significativamente de las formulaciones de la piel de la invención, que excluyen ciertos alergen^{os} e irritantes.

La técnica anterior no ha podido proporcionar una formulación del cuidado de la piel que evite ingredientes irritantes y alergen^{icos} pero que retengan las propiedades favorables, en particular en el campo médico del cuidado de la piel. Esto puede atribuirse al hecho de que el evitar estrictamente tales ingredientes afecta otras propiedades deseadas tal como humedad efectiva de la piel seca, estabilidad de la formulación y atributos sensoriales favorables desde el punto de vista del paciente/consumidor.

Por consiguiente, existe la necesidad de una formulación del cuidado de la piel hipoalergénica y no irritante que efectivamente humecte la piel sensible seca mientras que al mismo tiempo muestren una estabilidad física/microbiológica y cumpla con las expectativas estéticas subjetivas del paciente/consumidor.

Objeto y Resumen de la Invención

Es un objeto de la presente invención solucionar los

problemas asociados con las formulaciones del cuidado de la piel disponibles y conocidas proporcionando una formulación del cuidado de la piel hipoalergénica y no irritante. A parte de ser hipoalergénica y no irritante, la formulación de la invención efectivamente humecta la piel sensible seca y es estable y agradable para el paciente/consumidor. Las formulaciones de la invención son adecuadas para los cuidados médicos de la piel, tal como para la terapia o apoyo de terapia de la psoriasis y eczema.

10 Las formulaciones de la invención no tienen ←
ingredientes tal como perfumes o sustitutos de perfume (fragancia), conservadores, colorantes, extractos vegetales, glicoles polietilénicos (los PEG), alcohol cetilestearílico, alcoholes lanolínicos, alcoholes bajos, proteínas y otras
15 sustancias con potencial alergénico conocido, de este modo son particularmente adecuadas para pacientes con piel sensible. Sin embargo, se deberá notar que el término "sin ingredientes con potencial alérgico conocido" pretende significar que tal sustancia no se incluye a propósito en las formulaciones,
20 aunque pueden estar presentes en cantidades muy limitadas, por ejemplo, tal como contaminantes de otros ingredientes. Ya que el potencial alergénico y/o irritante de los ingredientes generalmente se conoce que depende de su concentración, deberá entenderse que la presencia de cantidades muy limitadas de
25 tales ingredientes aún significa estar dentro del alcance de la

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presente invención.

Las formulaciones de la invención comprenden una fase acuosa dispersa en una fase de aceite. En esta modalidad, la fase de aceite puede comprender octanoato cetearílico, éter dicaprilílico, triglicérido caprílico/cáprico, poligliceril-3-diisoestearato y poligliceril-2-dipolihiidroxiestearato.

En un aspecto de la invención, las formulaciones tienen relativamente pocos ingredientes, de preferencia menos de 15, más preferiblemente 12 ó 13 ingredientes.

En otro aspecto de la invención, la fase acuosa de las formulaciones comprende los ingredientes de agua purificada, sulfato de magnesio, ácido láctico y lactato de sodio. Adicionalmente, la fase acuosa puede además comprender glicerina.

En una modalidad, la fase de aceite de la formulación puede además comprender petrolato y cera alba. Adicionalmente, la fase de aceite puede comprender etilhexilglicerina o, alternativamente, la fase acuosa puede además comprender propilenglicol.

En una segunda modalidad, la fase de aceite puede además comprender etilhexilglicerina. En esta segunda modalidad, la fase acuosa puede además comprender urea.

La invención además proporciona un método para fabricar las formulaciones del cuidado de la piel hipoalergénicas y no irritantes de la invención. También

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proporciona formulaciones comprendiendo adicionalmente uno o más compuestos farmacéuticamente activos, vitaminas o análogos de vitaminas y/o un protector solar, así como también formulaciones que se utilizan en la profilaxis y el tratamiento de piel seca sensible o en la terapia de piel eczematosa o psoriática.

Es otro objeto de la invención proporcionar un método para la profilaxis y el tratamiento de piel seca sensible o para apoyo de terapia de la piel eczematosa o de la piel psoriática o tópicamente administrando una cantidad terapéuticamente efectiva de las formulaciones del cuidado de la piel dermatológica de la presente invención.

Descripción Detallada de la Invención

La invención proporciona formulaciones del cuidado de la piel hipoalergénicas y no irritantes que tienen propiedades superiores? Las formulaciones de la invención, modalidades ejemplares de las cuales se describirán con detalle más adelante, son particularmente adecuadas para el cuidado médico de la piel y para el tratamiento de piel sensible seca. A pesar de no tener tales ingredientes tal como perfumes o sustitutos de perfumes, conservadores, colorantes, extractos de planta, Los PEG, alcohol cetilestearílico, alcohol lanolínico, alcoholes bajos, y proteínas, las formulaciones de la invención inesperadamente retienen muchas propiedades deseables.



Aunque muchos de los ingredientes comúnmente utilizados en las formulaciones del cuidado de la piel no están presentes, las formulaciones del cuidado de la piel de la invención son altamente efectivas con una tolerancia a la piel máxima. Para las formulaciones, se escogieron materias primas con una tolerancia a la piel probada y una alta estabilidad fisicoquímica y microbiológica. Enfocándose en las propiedades de los ingredientes individuales, se seleccionó una mezcla de lípidos de piel con base en las propiedades sensoriales, tacto y polaridad. Además, para poder solucionar los problemas de la técnica anterior, sustancias con potenciales alergénicos o irritantes conocidas se eliminaron y solo ingredientes seleccionados, de preferencia con propiedades multifuncionales, tipos modernos de emulsificantes biodegradables fueron empleados. Estas formulaciones exhiben un alto grado de dispersidad y son adecuadas para la aplicación en la zona de clima IV.

Aunque son adecuadas para uso médico, las formulaciones del cuidado de la piel de la invención tienen propiedades cosméticas favorables, tal como excelente absorción, carencia de pegajosidad, fragancia y brillosidad aceitosa. Esto se puede evidenciar por los resultados de los estudios de valoración sensoriales realizados con varias modalidades de la invención (véase Tabla 3).

ventajas

Las formulaciones de la invención además muestran una

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estabilidad física/microbiológica excelente (véase Ejemplo 4) y cumple con los requerimientos de las directivas cosméticas de la Unión Europea y los Estados Unidos. Las formulaciones son fisicoquímicamente estables y cumplen con los requerimientos de United States Pharmacopeia (USP) en términos de estabilidad microbiológica. Aunque no tiene conservadores, se puede esperar una vida de anaquel de por lo menos 2 años para las formulaciones de la invención.

En una modalidad preferida de la presente invención, la formulación del cuidado de la piel se encuentra en la forma de una formulación semisólida (crema), que es particularmente adecuada para la aplicación tópica sobre la cara. Tal formulación de preferencia es una emulsión W/O.

La siguiente tabla muestra los ingredientes de tal formulación preferida de la invención en donde cada ingrediente puede estar presente en una cantidad independientemente de la cantidad de los otros de acuerdo a los rangos dados en la tabla siguiente y expresados tal como porcentaje en peso (% p/p).

(a) fase de aceite		preferida	más preferida	mucho más preferida
petrolato	1 - 6%	2 - 5%	2.5 - 4%	2.75 - 3.5%
octanoato cetearílico	1 - 6%	2 - 5%	2.5 - 4%	2.75 - 3.5%
éter dicaprilílico	1 - 5%	1 - 3%	2 - 3%	2.5 - 3%

Triglicérido caprílico/capricho	4 – 12%	5 – 10%	7 – 9%	7.5 – 8.5%
Cera alba	0.5 – 4%	1.0 – 2.5%	1.5 – 2.5%	1.75 – 2.25%
Poligliceril-3-diisostearato	3 – 6%	4 – 5%	4.25 – 4.75%	4.4 – 4.6%
Poligliceril-2-dipolihiidroxiestearato	0.5 – 3%	1 – 2%	1.25 – 1.75%	1.4 – 1.6%
(B) fase acuosa				
glicerina	0 – 7%	0 – 5%	2 – 4%	2.5 – 3.5%
sulfato de magnesio	0.2 – 2%	0.5 – 1.5%	0.8 – 1.2%	0.9 – 1.1%
ácido láctico	0 – 2%	0.05 – 1.5%	0.05 – 0.5%	0.05 – 0.25%
lactato de sodio	0.5 – 6%	1 – 5%	1 – 3%	1 – 2.5%
propilenglicol	4 – 12%	5 – 10%	7 – 9%	7.5 – 8.5%
agua purificada	Adicional hasta 100%	Adicional hasta 100%	Adicional hasta 100%	Adicional hasta 100%

En una segunda modalidad preferida, la formulación semi-sólida (crema) comprende los siguientes ingredientes, en donde cada ingrediente puede estar presente en una cantidad independientemente de la cantidad de los otros ingredientes de acuerdo con los rangos proporcionados en la siguiente tabla y expresados tal como porcentaje en peso (% p/p).

(A) Fase de Aceite		preferida	más preferida	mucho más preferida
Petrolato	1 – 6%	2 – 5%	2.5 – 4%	2.75 – 3.5%
Octanoato cetearílico	1 – 6%	2 – 5%	2.5 – 4%	2.75 – 3.5%
Éter dicaprilílico	1 – 5%	1 – 3%	2 – 3%	2.5 – 3%

triglicérido caprílico/cáprico	4 - 12%	5 - 10%	7 - 9%	7.5 - 8.5%
cera alba	0.5 - 4%	1.0 - 2.5%	1.5 - 2.5%	1.75 - 2.25%
poligliceril-3-diisostearato	3 - 6%	4 - 5%	4.25 - 4.75%	4.4 - 4.6%
poligliceril-2-dipolihidroxiestearato	0.5 - 3%	1 - 2%	1.25 - 1.75%	1.4 - 1.6%
(b) fase acuosa				
glicerina	0 - 7%	0 - 5%	2 - 4%	2.5 - 3.5%
sulfato de magnesio	0.2 - 2%	0.5 - 1.5%	0.8 - 1.2%	0.9 - 1.1%
ácido láctico	0 - 2%	0.05 - 1.5%	0.05 - 0.5%	0.05 - 0.25%
lactato de sodio	0.5 - 6%	1 - 5%	1 - 3%	1 - 2.5%
propilenglicol	4 - 12%	5 - 10%	7 - 9%	7.5 - 8.5%
agua purificada	adicional hasta 100%	adicional hasta 100%	adicional hasta 100%	adicional hasta 100%

De preferencia, la formulación anterior es una emulsión W/O. También es particularmente adecuada para la aplicación sobre la cara.

En una tercera modalidad preferida de la invención, la formulación del cuidado de la piel se encuentra en la forma de una formulación semi-líquida (loción) (de preferencia W/O) que es adecuada para la aplicación tópica en todo el cuerpo. Cada ingrediente puede estar presente en una cantidad independientemente de la cantidad de los otros ingredientes de acuerdo con los rangos proporcionados en la siguiente tabla y expresados tal como porcentaje en peso (% p/p).

(a) fase de aceite		preferida	más preferida	mucho más preferida
octanoato cetearílico	1 – 8%	2 – 5%	3.5 – 5%	4.5 – 5%
éter dicaprilílico	1 – 5%	1 – 3%	2 – 3%	2.5 – 3%
triglicérido caprílico/capricho	6 – 20%	8 – 15%	12 – 15%	14 – 15%
poligliceril-3-diisostearato	1 – 4%	1.5 – 3%	1.75 – 2.25%	1.9 – 2.1%
poligliceril-2-dipolihidroxiestearato	2 – 6%	3 – 5%	3.5 – 4.5%	3.75 – 4.25%
etilhexilglicerina	0 – 1%	0 – 0.8%	0.2 – 0.6%	0.25 – 0.5%
(b) fase acuosa				
glicerina	0 – 6%	0 – 5%	2 – 4%	2.5 – 3.5%
sulfato de magnesio	0.25 – 2%	0.5 – 1.5%	0.8 – 1.2%	0.9 – 1.1%
ácido láctico	0 – 2%	0.05 – 1.5%	1 – 1.4%	1.2 – 1.3%
lactato de sodio	0.5 – 7%	1 – 5%	3 – 4.5%	3.25 – 4.25%
urea	0.5 – 12%	0.5 – 10%	3 – 7%	4 – 6%
agua purificada	adicional hasta 100%	adicional hasta 100%	adicional hasta 100%	adicional hasta 100%

Se deberá entender que los porcentajes o rangos de porcentaje antes mencionados proporcionados para los ingredientes de las formulaciones de acuerdo con la invención pueden estar sujetos a pequeñas variaciones (por ejemplo, debido a grados variables de pureza de los ingredientes) sin apartarse del espíritu de la invención.

Sin embargo, los ingredientes utilizados para las

formulaciones farmacológicas de la invención deberán ser de alta calidad y pureza.

Las formulaciones del cuidado de la piel hipoalergénicas y no irritantes de la invención son adecuadas como emolientes, para la terapia o apoyo de terapia de piel eczematosa y psoriática, así como también para el tratamiento del cuidado de la piel terapéutico diario de piel seca sensible.

Además, las formulaciones de la invención pueden además comprender uno o más de los ingredientes seleccionados de un protector solar, una vitamina o análogo de vitamina, tal como Vitamina E, Vitamina K, Calcipotriol, Tacalcitol, o un compuesto farmacéuticamente activo, tal como corticoides, antimicóticos, inmunosupresores, ácido salicílico, ácidos alfa- o beta-hidroxi, o ácido linoleico.

El grupo de corticoides puede incluir pero no se limita a hidrocortisona y derivados de la misma, tal como aceponato de metilprednisolona, valerato de diflucortolona, fluocortolona/pivalato/hexanoato/monohidrato, fluocortinbutilo, betametasona y derivados de los mismos, clobetasola, triamcinolona, acetonida, dexametasona, prednisolona, y pivalato de clocortolona. El grupo de antimicóticos puede incluir pero no se limita a cetoconazol, isoconazol, miconazol, y clotrimazol; y el grupo de inmunosupresores puede incluir pero no se limita a ascomicina y derivados de la misma,

ciclosporina A, azatioprina, metotrexato, ciclofosfamida, y similares.

La invención además proporciona un método contundente y de fácil aplicación para fabricar las formulaciones del cuidado de la piel de la invención. La fabricación de las formulaciones del cuidado de la piel se logran preparando la fase de aceite fundiendo los ingredientes de la fase de aceite tal como octanoato cetearílico, éter dicaprílico, triglicérido caprílico/cáprico, poligliceril-3-diisostearato, poligliceril-2-dipolihiidroxiestearato, petrolato, cera alba, y etilhexilglicerina, con agitación hasta que todos los ingredientes se fundan completamente. Los ingredientes elegidos para la fase de aceite dependerán de la fase de aceite deseada, como se describió anteriormente.

Para la fase (acuosa), el agua purificada se calienta en un recipiente separado y los ingredientes de la fase acuosa, sulfato de magnesio, lactato de sodio, ácido láctico, y opcionalmente glicerina, urea y propilenglicol, se adicionan dependiendo de la composición deseada de la fase acuosa (véase lo anterior, por ejemplo). Tales ingredientes se disuelven agitando y subsecuentemente, el valor de pH de la solución resultante se ajusta con ácido láctico a aproximadamente 4.4 - 4.8. Tanto la fase acuosa como la de aceite de preferencia se calientan a aproximadamente 75 - 85°C durante la fusión y la disolución, respectivamente.

Antes de la combinación de la fase acuosa y de aceite, la fase de aceite se filtra a través de cartuchos de filtro con unidades de filtro de 0.1 mm para filtración de partículas. Subsecuentemente, la emulsión se prepara transfiriendo la fase de aceite fundida como se preparó anteriormente a la fase acuosa calentada y, mientras se agita y se homogeniza, enfriar la emulsión hasta condiciones de vacío, de preferencia de aproximadamente -0.6 a -0.9 bar, a temperatura ambiente.

De preferencia, la fase de aceite se transfiere a la fase acuosa mientras que se agita a aproximadamente 40 min⁻¹ a 75 - 85°C, se enfría hasta aproximadamente 58 - 62°C mientras que se agita y homogeniza a 3000 min⁻¹, se enfría adicionalmente hasta aproximadamente 38 - 42°C mientras que se agita y homogeniza a 4000 min⁻¹, y finalmente se enfría hasta aproximadamente 23 - 27°C mientras que se agita. Después del proceso de enfriamiento, las emulsiones de W/O semi-sólidas o semi-líquidas preparadas de la presente invención pueden depositarse en recipientes apropiados.

La invención se ilustra adicionalmente en los Ejemplos. Los Ejemplos no pretenden limitar el alcance de la invención.

Ejemplo 1: Preparación de la formulación A semi-sólida

Una formulación semi-sólida de acuerdo con la

invención (designada como Formulación A, a continuación) se preparó en tamaño de lote de 50 kg utilizando un homogenizador y mezcladora de ungüento (disponible bajo el nombre comercial Becomix® RW 60 de Berents, Alemania), equipado con una charola de acero inoxidable de 60 L, un agitador tipo ancla infinitamente variable, homogenizador y un sistema de control de proceso, medidor de pH, charola de porción de acero inoxidable equipada con un agitador infinitamente variable, recipientes de almacenamiento de acero inoxidable para ungüento, y cartuchos de filtro sinterizados de acero inoxidable, 0.1 mm para filtración de partículas.

Para la preparación de la fase acuosa, se cargó el homogenizador/mezcladora de ungüento con 33.7 kg de agua purificada, 1.5 kg de glicerina, 0.5 kg de sulfato de magnesio, y 0.992 kg de lactato de sodio y se agitó (40 min^{-1}) a $80 \pm 2^\circ\text{C}$ hasta que todos los componentes se disolvieron por completo. Subsecuente, el valor de pH se revisó y se ajustó con 0.058 kg de ácido láctico a un pH de aproximadamente 4.6.

La fase de aceite se preparó cargando el recipiente de porción con 1.5 kg de petrolato, 1.5 kg de octanoato cetearílico, 1.5 kg de éter dicaprilílico, 4.0 kg triglicérido caprílico/cáprico, 1.0 kg de cera alba, 2.25 de poligliceril-3-diisoestearato, 0.75 kg de poligliceril-2-dipolihidroxiestearato, y 0.15 kg de etilhexilglicerina y se fundió completamente a $80 \pm 2^\circ\text{C}$ mientras que se agitó hasta que

no hubo material no fundido visible. Finalmente, la fase de aceite de filtró a través de los cartuchos de filtro de acero inoxidable con unidades de filtro de 0.1 mm para filtración de partículas antes de adicionarla a la fase de agua.

5 La emulsión se preparó subsecuentemente transfiriendo la fase de aceite a la fase acuosa en la mezcladora/homogenizadora de ungüento con agitación a (40 min^{-1}) a $80 \pm 2^\circ\text{C}$. La mezcla resultante entonces se enfrió a $60^\circ \pm 2^\circ\text{C}$ mientras que se agitó y homogeneizó (ciclo 3000 min^{-1}). La
10 emulsión resultante entonces se agitó y se homogeneizó adicionalmente (ciclo de 4000 min^{-1}) durante el enfriamiento a $40^\circ \pm 2^\circ\text{C}$. Finalmente, la agitación de la emulsión continúa hasta que la emulsión obtuvo una temperatura de $25^\circ \pm 2^\circ\text{C}$. Durante el proceso de enfriamiento completo se aplicó un vacío
15 de entre -0.6 y 0.9 bar.

Se revisó la homogeneidad por apariencia uniforme de la crema resultante por medio de microscopía. Después de pasar esta prueba de homogeneidad, el producto fue vertido en contenedores de volumen.

20

Ejemplo 2: Preparación de formulación B semi-sólida

La formulación B fue preparada igual que la formulación A, con la excepción de que se adicionaron 4 kg de propilenglicol a la fase acuosa y no se adicionó
25 etilhexilglicerina a la fase de aceite.

Ejemplo 3: Preparación de formulación C semi-sólida

La formulación C semi-líquida fue esencialmente preparada igual que las formulaciones A y B en los Ejemplos 1 y 2. Las diferencias en los procesos de fabricación se describirán más adelante.

Para la producción de la formulación C en un tamaño de lote de 50 kg, la mezcladora /homogeneizadora de ungüento se cargó con 28.35 kg de agua purificada, 1.5 kg de glicerina, 0.5 kg de sulfato de magnesio, 1.867 kg de lactato de sodio, y 2.5 kg de urea y se agitó (40 min^{-1}) a $80 \pm 2^\circ\text{C}$ hasta que todos los componentes se disolvieron por completo. Subsecuentemente, el valor del pH se verificó y se ajustó con 0.633 kg de ácido láctico a un pH de aproximadamente 4.2.

La fase de aceite se preparó cargando el recipiente de fusión con 2.5 kg de octanoato cetearílico, 1.5 kg de éter dicaprilílico, 7.5 kg triglicérido caprílico/cáprico, 1.0 kg de poligliceril-3-diisoestearato, 2.25 kg de poligliceril-2-dipolihiidroxiestearato, y 0.15 kg de etilhexilglicerina y se fundió completamente a $80 \pm 2^\circ\text{C}$ mientras que se agitó hasta que no hubo material sin fundir visible.

Después de la filtración en partículas, ambas fases se combinaron para formar una emulsión como se describe en el Ejemplo 1. Después de pasar la prueba de homogeneidad, la loción resultante se vertió en contenedores de volumen.

Ejemplo 4: Estabilidad microbiológica/fisicoquímica

Las formulaciones A, B, y C como se prepararon en los Ejemplos 1 a 3 se sometieron a las siguientes pruebas de estabilidad:

- 5 a) Almacenamiento a 4°C, 25°C, 30°C, 40°C, 50°C a una humedad ambiental durante 5 meses
- b) prueba de ciclo de -4°C/50°C durante dos semanas
- c) La prueba de reto microbiológico de acuerdo con los requerimientos de USP (United States Pharmacopeia)
- 10

Las formulaciones se empacaron en contenedores PE (HDPE/LDPE) en tamaños de lote de 2 - 25 kg y se probaron por parámetros tal como valor de pH, viscosidad (abs.), imagen microscópica y macroscópica, contenido de urea (formulación C),

15 y compatibilidad con el material del contenedor.

Los resultados de las pruebas mostraron que las formulaciones A-C de los Ejemplos 1-3 son fisicoquímicamente estables bajo todas las condiciones probadas y cumplen con los requerimientos de estabilidad microbiológicos de USP.

20

Ejemplo 5: Riesgo de irritación y sensibilidad (Prueba - HRIPT)

Se llevó a cabo una prueba de parche de agresión repetida humana (HRIPT) tal como un estudio de doble ciego controlado aleatorio de 40 días para evaluar el potencial de

25 irritación y sensibilidad en las formulaciones dermatológicas

del cuidado de la piel de la invención. El estudio comenzó con 58 voluntarios sanos de cualquier sexo entre 18 y 65 años (casos en ITT: n= 58), sin embargo, tres voluntarios desertaron y 55 voluntarios completaron el estudio (caos de VC: n= 55).

5 En la fase de inducción (día 1 - 20), los voluntarios fueron sometidos a nueve tratamientos de oclusión durante 24 horas con 75 µl de las formulaciones de prueba tal como se prepararon en los Ejemplos 1-3 aplicadas en la espalda en los días 1, 3, 5, 8, 10, 12, 15, 17, 19. Los campos de prueba no
10 tratados sin aplicación de la formulación de prueba se utilizaron tal como control concurrente. Las reacciones de la piel se evaluaron 24 horas (1/2 hora después de la remoción de las cámaras de prueba; en los días 2, 4, 6, 9, 11, 13, 16, 18, 20; nueve lecturas) y 48 horas después de la aplicación de los
15 tratamientos de oclusión en las espaldas de los voluntarios (1/2 hora después de la remoción de las cámaras de prueba en los días 3, 5, 10, 12, 17, 19; seis lecturas) por medio de una calificación visual de 6 puntos.

20

Calificación visual de 6 puntos	
0	Negativo/sin reacción

25

0.5	Eritema dudoso
1	Eritema
2	Eritema e induración (edema)
3	Eritema, induración (edema y vesículas)
4	Eritema, induración (edema) y ampollas, y/o diseminación

El índice de irritación acumulativo promedio (M.C.I.I.) se calculó para las lecturas de 24 horas (M.C.I.I./24 h.) y para las lecturas de 48 horas (M.C.I.I./48 h.).

Después del intervalos sin tratamiento (15 días; días 21-35; sin tratamiento), se hizo una aplicación de reto de oclusión de las formulaciones de prueba en sitios de prueba aún no atrapados de la espalda de los voluntarios durante 24 horas. Las formulaciones se prueba se evaluaron en 24 h, 48 h, 72 h, y 96 h después de la aplicación por la misma calificación visual de 6 puntos (fase de reto; 5 días, días 36-40).

Resultados:

Sensibilidad: No ocurrió ningún caso de sensibilidad ni en la población ITT ni en la población VC.

Irritación: No se observó irritación potencial significativa en comparación con el campo de prueba no tratado vacío en la población ITT ni en la población VC.

Además, no se observaron eventos adversos o eventos adversos serios relacionados con las formulaciones de prueba durante el curso del estudio.

5 Ejemplo 6: Potencial de Irritación

El objetivo principal de este estudio puede evaluar la tolerancia cutánea de las formulaciones del cuidado de la piel de la invención durante un periodo de cuatro semanas cuando se utilizan en la manera pretendida (aplicación de dos veces al día en la cara o cuerpo, respectivamente) en el grupo de pacientes/consumidores pretendido teniendo piel sensible y seca. Los objetivos secundarios de este estudio pueden evaluar el potencial de irritación de las formulaciones de prueba A y B utilizándolas alrededor de los ojos, para evaluar el efecto de hidratación de todas las formulaciones de prueba tal como se mide por corneometría, para evaluar la aceptación cosmética general de los voluntarios de todas las formulaciones de prueba, y finalmente evaluar la aceptación cosmética de las formulaciones de prueba A y B tal como bases de maquillaje.

20 El estudio fue diseñado tal como un estudio aleatorio de un solo centro; de doble ciego con comparación inter-individual de tratamientos entre las formulaciones de prueba A, B y productos comercialmente disponibles comparativos para la aplicación facial y entre la formulación de prueba C y los
25 productos comercialmente disponibles comparativos para la

aplicación corporal, y se realizaron durante 28 días consecutivos.

////Voluntarios sanos de ambos sexos entre 18 y 65 años de edad que cumplen con el criterio de inclusión/exclusión específico con piel seca probado por valores de corneometría
5 bajos (≤ 70) se escogieron para este estudio. Además, 50% de los voluntarios eran individuos sanos con diatesis atópica de acuerdo con la calificación de atopia de Diepgen sin un historial de dermatitis atópica. En otro 50% de los voluntarios
10 no sufrían de diatesis atópica. Todos los voluntarios en todos los grupos de tratamiento fueron tratados en la cara y el cuerpo dos veces al día en casa durante 28 días consecutivos con formulaciones de prueba respectivas. Para la medición de los efectos de hidratación de las formulaciones de prueba para
15 la aplicación facial, la corneometría de ambos pómulos se realizó en los días 1 y 29. Para la formulación de prueba para la aplicación corporal se realizó la corneometría de ambas piernas inferiores anteriores en pantalla y en los días 1 y 29.

Una valoración clínica se realizó en pantalla en los
20 días 1, 8, 15 y 29 utilizando una calificación visual de 5 puntos (signos de irritación ninguno, dudoso, ligero, moderado, severo, eritema y/o escamación). A raíz de los resultados de la calificación visual de 5 puntos se creo un perfil de producto de irritación con cuatro grupos de irritación siendo la
25 variable principal de este estudio. Se preguntó a cerca de los

internos subjetivos en los días 8, 15 y 29 utilizando una calificación de 5 puntos para una evaluación subjetiva (sensación ninguno/dudosa/ligera/moderada/severa de picazón/quemazón/pruritus con especificación en caso de cualquier respuesta positiva). Adicionalmente, se llevaron a cabo exámenes oftalmológicos que estudiaron la parte anterior y posterior de los ojos así como también la mucosa conjuntiva y síntomas oftalmológicos subjetivos utilizando una calificación de 5 puntos para síntomas oftalmológicos subjetivos en los días 1 y 29.

Adicionalmente, los voluntarios llenarán un cuestionario en el día 29 relacionado con el perfil sensorial de la aceptación cosmética general (parámetros: distribución/propagación/absorción, sensación sobre la piel, pegajosidad, adiposidad, brillo aceitoso, olor, y color; evaluándolos en una escala de 5 puntos).

Resultados:

La Tabla 1 resume el efecto de hidratación tal como se mide por la corneometría de las tres modalidades de la invención (formulaciones A, B, y C) en comparación con un producto de referencia.

Tabla 1: Medición de Efecto de Hidratación por Corneometría

Efecto de hidratación (Corneometría)	Mejoría de hidratación en el día 29 (en %) subgrupo I (sujetos atópicos)	Mejoría de hidratación en el día 29 (en %) subgrupo II (sujetos no atópicos)	Mejoría de hidratación en el día 29 (en %) subgrupo I + II
Formulación A (crema)	43.1	21.0	32.1
Formulación B (crema)	31.2	39.1	35.1
Formulación C (leche)	38.6	45.7	42.2 ✓
Producto de referencias	37.1	22.2	29.7

medido por corneometría de ambos pómulos (Formulaciones A y B) y ambas piernas inferiores anteriores (Formulación C), respectivamente

§ emulsión W/O comercialmente disponible

Adicionalmente, la aplicación de las formulaciones de prueba A, B y C durante 28 días da tal como resultado una mejoría de hidratación significativa entre 32% y 42%, promediando ambos subgrupos (sujetos atópicos y no atópicos).

Los resultados del estudio de tolerancia cutánea de las formulaciones A, B, y C se resumen en el Tabla 2. Las Tablas 2(a) y (b) muestran los resultados de los estudios dermatológicos y oftalmológicos, respectivamente.

Tabla 2: Resultados del Estudio de Tolerancia (Potencial de Irritación)

Tabla 2(a): Investigación Dermatológica:

26

Investigación Dermatológica (ITT)	Formulaciones para Cara		Formulación para Cuerpo
	Formulación A	Formulación B	Formulación C
(1) Perfil de irritación: signos objetivo	1/20 pacientes:	1/20 pacientes:	-
(2) discontinuación parcial o transitoria del tratamiento relacionado o posiblemente relacionado con la formulación de prueba	irritación moderada y discontinuo tratamiento en día 14	irritación ligera; reducción de la dosis de tratamiento	-
Signos objetivos de irritación: (1) + (2)	5% (1 paciente)	5% 1 paciente	-
(3) Perfil de irritación, síntomas subjetivos	1/20 pacientes: picazón ligera	2/20 pacientes: urticaria ligera 1/20 pacientes: picazón ligera	2/19 pacientes: urticaria ligera
Signos subjetivos de irritación: (3) reacciones moderadas o severas			-
Suma promedio de la calificación de irritación	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00
Conclusión	Perfil de irritación muy bueno	Perfil de irritación ? excelente	Perfil de irritación excelente

Tabla 2(b): Estudio Oftalmológico

Investigación Oftalmológica	Formulación para Cara		Formulación para Cuerpo
	Formulación A	Formulación B	Formulación C
Síntomas objetivos, oftalmológicos	1/20 pacientes: Alergia conjuntiva moderada del ojo izquierdo y alergia conjuntiva ligera del ojo derecho*	-	

Síntomas objetivos, oftalmológicos	1/20 pacientes: síntomas subjetivos moderados*	1/20 pacientes: urticaria ligera lagrimeo de ojo izquierdo*	Formulación para cuerpo no probada alrededor de los ojo
Aplicación interrumpida debido a síntomas oftalmológicos	-	-	
Conclusión	Tolerancia excelente de las formulaciones aplicadas alrededor de los ojos		

*Estudios subsecuentes demostraron que los síntomas anteriores no fueron causados por las Formulaciones A y B.

Tal como es evidente a partir de los resultados tabulados, todas las formulaciones dermatológicas probadas de la invención mostraron un perfil de irritación muy bueno o aún
5 excelente.

Adicionalmente, los resultados del cuestionario relacionado con la aceptación cosmética de las formulaciones A, B y C se representan en los Tablas 3(a)-(i). Los siguientes parámetros fueron probados: calidad cosmética general (Tabla
10 3(a)); distribución/propagación (Tabla 3(b)); absorción (Tabla 3(c)); sensación sobre la piel (Tabla 3(d)); pegajosidad (Tabla 3(e)); adiposidad (Tabla 3(f)); brillo aceitoso (Tabla 3(g)); olor (Tabla 3(h)); color (Tabla 3(i)).

15 Tabla 3: Resultados de las pruebas de valoración sensoriales

Todos los valores están dados en % de voluntarios.

Tabla 3(a): Opinión general de las cualidades cosméticas de las formulaciones A - C

Opinión General	Excelente	Muy buena	Buena	Aceptable	Mala	Sin comentario
Formulación A (crema)	16	42 ✓	32	5	5	0
Formulación B (crema)	15	10	45 ✓	5	10	15
Formulación C (crema)	26	16	37 ✓	5	11	5

Tabla 3(b): Distribución/Propagación

Distribución/propagación	Muy fácil	Fácil	Moderadamente	Difícil	Muy difícil
Formulación A (crema)	16	26	26	5	26
Formulación B (crema)	30	0	30	20	20
Formulación C (loción)	11	5	16	11	58

Tabla 3(c): Absorción

Absorción	Muy rápida	Rápida	Bastante rápida	Lenta	Muy lenta	Sin comentario
Formulación A (crema)	26	11	26	11	26	0
Formulación B (crema)	30	15	10	15	25	5
Formulación C (loción)	21	0	11	21	47	0

Tabla 3(d): Sensación sobre la piel

Sensación sobre la piel	Demasiado ligera	Ligera	Perfecta	Pesada	Muy pesada
Formulación A (crema)	11	5	26	21	37
Formulación B (crema)	10	5	30	25	30
Formulación C (loción)	5	5	11	21	58

Tabla 3(e): Pegajosidad

Pegajosidad	Nada pegajosa	Poco pegajosa	Ligeramente pegajosa	Bastante pegajosa	Pegajosa
Formulación A (crema)	26	5	37	11	21
Formulación B (crema)	15	10	45	15	15
Formulación C (loción)	0	0	26	32	42

Tabla 3(f): Adiposidad

Adiposidad	Nada grasosa	Poco grasosa	Ligeramente grasosa	Bastante grasosa	Grasosa
Formulación A (crema)	11	5	32	42	11
Formulación B (crema)	15	0	20	55	10
Formulación C (loción)	5	5	26	63	0

Tabla 3(g): Brillo aceitoso

Brillo aceitoso	No deja brillo aceitoso	Deja muy ligero brillo aceitoso	Deja ligero brillo aceitoso	Deja brillo aceitoso	Deja mucho brillo aceitoso	Sin comentario
Formulación A (crema)	21	5	21	37	16	
Formulación B (crema)	15	0	25	20	40	
Formulación C (loción)	16	0	11	37	32	5

Tabla 3 (h): Olor

Olor	Ninguno	Si, muy ligero	Si, ligero	Si, moderado	Si, fuerte	Si, muy fuerte
Formulación A (crema)	53	16	21	0	5	5
Formulación B (crema)	40	35	15	5	5	0
Formulación C (loción)	58	21	16	5	0	0

Tabla 3(i): Color

Color	Muy agradable	Agradable	Desagradable	No importa	Sin comentario
Formulación A (crema)	16	53	16	16	0
Formulación B (crema)	20	45	15	20	0
Formulación C (loción)	16	53	26	5	0

Ejemplo 7: Fototoxicidad

Para poder evaluar el potencial fototóxico de las formulaciones dermatológicas para el cuidado de la piel de la invención, las formulaciones semi-sólidas del ejemplo 1 y 2 se probaron en el estudio de fototoxicidad durante 5 días consecutivos. El estudio se diseñó tal como un estudio doble ciego aleatorio de un solo centro con comparación individual de tratamientos y comparación inter-dividual de tratamientos para las formulaciones de prueba A y B. Se enlistaron a 12 voluntarios solos de ambos sexos entre 18 y 50 años de edad que confían con el criterio de inclusión/exclusión específico en el estudio. Se aplicaron 50 µl de cada formulación de prueba bajo condiciones de oclusión por duplicado en la espalda de los sujetos en los días 1 durante 24 horas. Un campo de prueba duplicado sin aplicación de las formulaciones (cámara de prueba

vacía con/sin radiación UV) se utilizó tal como control.

En el día 1 y 2, se valoró la dosis de eritema mínima (MED) por irradiación de seis campos de prueba pequeños con UVA/B en la espalda superior del voluntario. Las cámaras de prueba con las formulaciones de prueba por duplicado se aplicaron en día 1 a los campos de prueba designados en ambos lados de la espalda media de los voluntarios. En el día 2, las cámaras de prueba se removieron después de 24 horas y los campos de prueba ($20 \text{ J/cm}^2 \text{ UVA} + 0.75 \times \text{MED UVA} + \text{UVB}$) fueron irradiados en el lado izquierdo de la cara de la espalda media. Las reacciones de piel fueron valoradas después de una hora (día 2), después de 24 horas (día 3), después de 48 horas (día 4) y después de 72 horas (día 5) utilizando una calificación de punto visual:

Calificación visual de 5 puntos	
0	Sin eritema
0.5	Eritema dudoso (eritema casi imperceptible sin clara delineación definida)
1	Eritema ligero pero definido con delineación claramente definida
2	Eritema moderada claramente definida
3	Eritema severo con o sin filtración
4	Eritema severo con vesículas o reacción vejigosa

El número de voluntarios que experimentó una reacción fototóxica durante el estudio determinó el potencial fototóxico en las formulaciones de prueba.

Resultados: No se pudo observar ningún caso de fototoxicidad con las formulaciones farmacológicas A y B durante el estudio en la formulación de prueba.

5

Ejemplo 8: Riesgo de Foto-Sensibilidad

El objetivo principal de este estudio puede evaluar el potencial de fotosensibilidad de las formulaciones dermatológicas de la invención en una población de n=25 voluntarios sanos de ambos sexos entre 18 y 65 años con tipo de piel Fitzpatrick I, II, o III que cumplieron con el criterio específico de inclusión/exclusión utilizando el método modificado de Kaidbey & Kligman (Kaidbey & Kligman, 1980, *Contact Dermatitis* 6, 161-169). El objetivo secundario de este estudio fue evaluar el potencial de sensibilidad de las formulaciones.

El estudio fue diseñado tal como un estudio de un estudio doble ciego aleatorio de un solo centro con comparación intra-individual de tratamientos en comparación inter-individual de tratamientos para las formulaciones de prueba incluyendo las formulaciones A y B (crema) y se realizó durante 6 semanas consecutivas. Tal como control, los campos de prueba no tratados sin la aplicación de formulaciones de prueba se incluyeron en el estudio.

25

Durante la fase de inducción, una serie de plastas de

prueba con todas las formulaciones de prueba y un campo vacío se fijaron en los lados izquierdo de la espalda. Durante la fase de reto, dos series de plastas de prueba se fijaron en cada lado de la espalda. Solo el lado derecho de la espalda fue irradiado. La asignación de las formulaciones de prueba a los campos de prueba fue idéntica para cada voluntario durante la inducción y la fase de reto. Para cada aplicación, se aplicaron 50 µl de la formulación de prueba bajo condiciones de oclusión en las espaldas de los voluntarios en los días 1, 4, 8, 11, 15, 18 y 36.

La MED de cada sujeto se determinó irradiando dosis incrementadas de UVA/UVB/ con un simulador solar en sitios previamente seleccionados de las espaldas de los voluntarios. Se llevó a cabo la calificación 24 horas después de la irradiación. La MED es la dosis más pequeña (mJ/cm^2) necesaria para inducir un eritema claramente delineado visible.

En la fase de inducción (20 días; día 1-20), aplicaciones de oclusión de una serie de formulaciones de prueba se realizaron durante 24 horas en el lado izquierdo de las espaldas de los voluntarios en los días 1, 4, 8, 11, 15, 18. Después de 24 h, los tratamientos de oclusión se removieron y todos los campos de prueba se expusieron consecutivamente a 3 x MED UVA/UVB con un simulador solar en los días 2, 5, 9, 12, 16 y 19. Los resultados se evaluaron 24 horas después en la irradiación por una calificación visual de seis puntos.

En la fase de reto (5 días; día 36-40) después del intervalo sin tratamiento (15 días; día 21-35), aplicación de oclusión de dos series de formulaciones de prueba en o un sitio no tratados en ambos lados de las espaldas de los voluntarios se realizó durante 24 horas (aplicación de reto). Consecutivamente, los campos de prueba se expusieron en el lado derecho de las espaldas a 10 J/cm^2 UVA más $0.75 \times \text{MED}$ (UVA/UVB) (irradiación de reto en el día 37). Los resultados se evaluaron una hora después en la irradiación de reto y adicionalmente 24 h, 48 h y 75 h después de la irradiación de reto por una calificación visual de 6 puntos.

La siguiente calificación visual de 6 puntos se utiliza durante la fase de reto y de inducción:

Calificación visual de 6 puntos	
0	Sin eritema
0.5	Eritema dudoso
1	Eritema definitivo con delineación claramente definida (MED)
2	Eritema con filtración/ barro
3	Eritema con vesículas o reacción vejigosa
4	Eritema con reacción vejigosa erosionada y/o reacción de diseminación elevada más allá de los límites del sitio del parche

Resultados: No se observaron casos de fotosensibilidad bajo las condiciones anteriormente descritas para las formulaciones dermatológicas A y B del Ejemplo 1 y 2 (formulaciones faciales) en ninguno de los voluntarios.

REIVINDICACIONES

1. Una formulación del cuidado de la piel hipoalergénica no irritante, en donde la formulación:

a) no tiene fragancias, conservadores, colorantes, extractos vegetales, Los PEG, alcohol cetilestearílico, alcohol lanolínico, alcoholes bajos y proteínas; y

b) comprende una fase acuosa dispersa en una fase de aceite, en donde la fase de aceite comprende octanoato cetearílico, éter dicaprilílico, triglicérido caprílico/cáprico, poligliceril-3-diisostearato y poliglicerilo-2-dipolihiidroxiestearato.

2. La formulación del cuidado de la piel de acuerdo con la reivindicación 1, en donde la formulación tiene un número total de ingredientes que es menor a 15.

3. La formulación del cuidado de la piel de acuerdo con las reivindicaciones 1-2, en donde la fase acuosa comprende los ingredientes de agua purificada, sulfato de magnesio, ácido láctico y lactato de sodio.

4. La formulación del cuidado de la piel de acuerdo con las reivindicaciones 1-3, en donde la fase agua además comprende glicerina.

5. La formulación del cuidado de la piel de acuerdo con las reivindicaciones 1-4, en donde la fase de aceite además comprende etilhexilglicerina.

6. La formulación del cuidado de la piel de acuerdo

con las reivindicaciones 1-4, en donde la fase de aceite de la formulación además comprende petrolato y cera alba.

7. La formulación del cuidado de la piel de acuerdo con la reivindicación 6, en donde la fase de aceite además
5 comprende etilhexilglicerina.

8. La formulación del cuidado de la piel de acuerdo con la reivindicación 6, en donde la fase acuosa además comprende glicol propilénico.

9. La formulación del cuidado de la piel de acuerdo
10 con las reivindicaciones 1-5, en donde la fase acuosa además comprende urea.

10. Una formulación semi-sólida para el cuidado de la piel que comprende los siguientes ingredientes expresados tal como un rango de porcentaje en peso (% p/p):

15 (I) fase de aceite:

a) petrolato:	2 - 5%
b) octanoato cetearílico:	2 - 5%
c) éter dicaprililílico:	1 - 3%
d) triglicérido caprílico/cáprico:	5 - 10%
20 e) cera alba:	1.0 - 2.5%
f) poligliceril-3-diisostearato:	4 - 5%
g) poliglicerilo-2-dipolihiidroxiestearato:	1 - 2%
h) etilhexilglicerina:	0 - 0.8%

(2) fase acuosa:

	a) glicerina:	0 - 5%
	b) sulfato de magnesio:	0.5 - 1.5%
	c) ácido láctico:	0.05 - 1.5%
5	d) lactato de sodio:	1 - 5%
	e) agua purificada:	adicionar hasta 100%

11. Una formulación semi-sólida para el cuidado de la piel, en donde la formulación comprende los siguientes ingredientes expresados tal como un rango de porcentaje en peso (% p/p):

(I) fase de aceite:

	a) petrolato:	2 - 5%
	b) octanoato cetearílico:	2 - 5%
	c) éter dicaprililico:	1 - 3%
15	d) triglicérido caprílico/cáprico:	5 - 10%
	e) cera alba:	1.0 - 2.5%
	f) poligliceril-3-diisostearato:	4 - 5%
	g) poliglicerilo-2-dipolihiidroxiestearato:	1 - 2%

(2) fase acuosa:

20	a) glicerina:	0 - 5%
	b) sulfato de magnesio:	0.5 - 1.5%
	c) ácido láctico:	0.05 - 1.5%
	d) lactato de sodio:	1 - 5%
25	e) propilenglicol:	5 - 10%

f) agua purificada: adicionar hasta 100%

12. Una formulación semi-líquida para el cuidado de la piel que comprende los siguientes ingredientes expresados tal como un rango de porcentaje en peso (% p/p):

5 (I) fase de aceite:

- | | |
|---|----------------------|
| a) octanoato cetearílico: | 2 - 5% |
| b) éter dicaprililílico: | 1 - 3% |
| c) triglicérido caprílico/cáprico: | 8 - 15% |
| d) poligliceril-3-diisostearato: | 1.5 - 3% |
| e) poliglicerilo-2-dipolihiidroxiestearato: | 3 - 5% |
| f) etilhexilglicerina: | adicionar hasta 100% |

(2) fase acuosa:

- | | | |
|----|-------------------------|----------------------|
| | a) glicerina: | 0 - 5% |
| 15 | b) sulfato de magnesio: | 0.5 - 1.5% |
| | c) ácido láctico: | 0.05 - 1.5% |
| | d) lactato de sodio: | 1 - 5% |
| | e) urea: | 0.5 - 10% |
| | f) agua purificada: | adicionar hasta 100% |

20 13. _La formulación para el cuidado de la piel de acuerdo con cualquier de las reivindicaciones 1-12, en donde la formulación además comprende uno o más compuestos farmacéuticamente activos, vitaminas y análogos de vitaminas, y/o bronceadores.

25 14. La formulación para el cuidado de la piel de

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acuerdo con la reivindicación 13, en donde el compuesto farmacéuticamente activo es un corticoide, un antimicótico, ácido salicílico, ácido alfa- o beta- hidroxí, y/o ácido linolénico; en donde la vitamina es Vitamina E, o Vitamina K; y en donde el análogo de vitamina es Cacipotriol o Tacalcitol.

15. La formulación para el cuidado de la piel de acuerdo con cualquiera de las reivindicaciones 1-14 que se utiliza en la profilaxis y tratamiento de piel sensible seca de la terapia de piel eczematosa y piel psoriática.

16. Un método para fabricar una formulación para el cuidado de la piel hipoalergénica y no irritante que comprende los pasos de:

- a) preparar una fase de aceite fundiendo los ingredientes de la fase de aceite tal como se define en cualquiera de las reivindicaciones 1, 5, 6, 7, ó 10 - 12;
- b) preparar una fase acuosa calentando el agua purificada y disolviendo dentro de la misma los ingredientes de la fase acuosa tal como se define en cualquiera de las reivindicaciones 3, 4, 8, ó 10 - 12 mientras que se agita y se ajusta al valor de pH de la solución resultante con ácido láctico a aproximadamente 4.4 - 4.8;
- c) preparar una emulsión de agua en aceite transfiriendo la fase de aceite fundida del paso (a) a la fase

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acuosa calentada del paso (b) y, mientras se agita y homogeniza, enfriar la emulsión hasta temperatura ambiente mientras que se aplica un vacío de aproximadamente -0.6 a -0.9 bar.

- 5 17. El método de acuerdo con la reivindicación 16, en donde el paso (a) y el paso (b) se realizan a una temperatura de aproximadamente 75 - 85°C y en donde el paso (c) comprende los pasos de transferir la fase de aceite del paso (a) a la fase acuosa del paso (b) mientras que se agita a
- 10 aproximadamente 40 min⁻¹ a 75 - 85°C, enfriando la emulsión hasta aproximadamente 58 - 62°C mientras que se agita y homogeniza a 3000 min⁻¹, enfriando la emulsión adicional hasta aproximadamente 38 - 42°C mientras que se agita y homogeniza a 4000 min⁻¹, enfriando la emulsión adicionalmente hasta
- 15 aproximadamente 23 - 27°C mientras que se agita, y se vierte la emulsión dentro de contenedores apropiados.

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RESUMEN

La invención proporciona formulaciones médicas para el cuidado de la piel hipoalergénicas y no irritantes novedosas siendo emulsiones de agua en aceite. Las formulaciones no
5 tienen ingredientes con potencial alergénico conocido, tal como fragancias, conservadores, colorantes, extractos vegetales, Los PEG, alcohol cetil estearílico, alcohol lanolínico, alcoholes bajos y proteínas, de este modo siendo particularmente adecuados para pacientes con piel seca sensible. Las
10 formulaciones para el cuidado de la piel de la invención son útiles en la profilaxis y tratamiento de la piel sensible seca o la terapia o apoyo de terapia de la piel eczematosa o psoriática y muestran propiedades sensoriales favorables. La invención además proporciona un método para fabricar las
15 formulaciones para el cuidado de la piel hipoalergénicas y no irritantes novedosas.

0	Para uso únicamente de la Oficina Receptora	
0-1	Solicitud Internacional No.	
0-2	Fecha de Presentación Internacional	
0-3	Nombre de la Oficina Receptora y "Solicitud Internacional PCT"	
0-4	Forma – Solicitud PCT PCT/RO/101	
0-4-1	Utilización preparada	PCT-EASY Versión 2.92 (actualizado 01.03.2001)
0-5	Solicitud El signatario solicitó que la presente solicitud internacional se procese de acuerdo al Tratado de Cooperación en Patente	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patente Europea (RO/EP)
0-7	Referencia de archivo del agente o solicitante.	SCH10130PCT
I	Título de la Invención	formulaciones para el cuidado de la piel hipoa-
II	Solicitante	genicas y no irritantes
II-1	Esta persona es:	Únicamente solicitante
II-2	Solicitante para	todos los Estados designados excepto US
II-4	Nombre	Schering AG
II-5	Dirección:	Müllerstrasse 178 D-13353 Berlin Alemania
II-6	Estado de nacionalidad	DE
II-7	Estado de residencia	DE
III-1	Solicitante y/o Inventor	
III-1-1	Esta persona es:	solicitante e inventor
III-1-2	Solicitante para	Únicamente US
III-1-4	Nombre	Franke, Patrick
III-1-5	Dirección:	McNair-Promenade 124 D14167 Berlin Alemania
III-1-6	Estado de nacionalidad	DE
III-1-7	Estado de residencia	DE
IV-1	Agente o representante común; o dirección para correspondencia Por la presente la persona identificada en lo siguiente es / ha sido nombrada para actuar a nombre de el o los solicitantes ante las Autoridades Internacionales competentes como:	agente
IV-1-1	Nombre (ULTIMO, Primero)	DF-MP DORRIES FRANK-MOLNIA & POHLMAN
IV-1-2	Dirección:	Triftstr. 13 D-80538 München Alemania
IV-1-3	Número Teléfono	089/2102960
IV-1-4	Número Facsímil	089/2109633
IV-1-5	e-mail	...@df-mp.com
V	Estados Designados	

V-1	Patente regional (otras clases de protección o tratamiento, si cualquiera, son especificados entre (después de la o las designaciones concernientes)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW y cualquier otro Estado Contratante de Protocolo de Harare y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado que sea un Estado Contratante del Convenio de la patente euroasiática y del PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR y cualquier otro Estado el cual es un Estado Contratante de la Convención de la Patente Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado el cual es un Estado miembro de la OAPI y que sea un Estado Contratante del PCT
V-2	Patente Nacional (otras clases de protección o tratamiento, si cualquiera, son especificados entre (después de la o las designaciones concernientes)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG, KP, KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
VI-1	Reclamo de prioridad de la solicitud nacional anterior.	
VI-1-1	Fecha de presentación	15 diciembre 2000 (15.12.2000)
VI-1-2	Numero	00127555.1
VI-1-3	País	EP
VI-2	Prioridad reivindicada de la solicitud nacional anterior	
VI-2-1	Ficha de presentación	15 diciembre 2000 (15.12.2000)
VI-2-2	Número	60/255,379
VI-2-3	País	US
VI-3	Solicitud de Documento de Prioridad La Oficina receptora esta solicitada para preparar y transmitir a la Oficina Internacional una copia certificada de la o las solicitudes anteriores identificadas en lo anterior como en o los puntos:	VI-1
VII-1	Elección de la Autoridad de Búsqueda Internacional	Oficina de Patente Europea (EPO) (ISA/EP)
VIII	explicaciones	numero de explicaciones
VIII-1	aclaración con respecto al inventor	1
VIII-2	aclaración con respecto a la legalidad del solicitante, en el momento de la fecha de Solicitud Internacional para presentar y obtener una Patente	-
VIII-3	explicación con respecto a la capacidad legal de Solicitante en el momento de la fecha de Solicitud Internacional para reivindicar la prioridad de una solicitud previa	-
VIII-4	aclaración del inventor (únicamente en vista de la aprobación en los Estados Unidos de América)	-
VIII-5	explicaciones con respecto a publicaciones que no hagan daño o excepciones de daño a la novedad	-
VIII-1-1	Aclaración: datos del inventor Aclaración a cerca de los datos del inventor (Regla 4.17 (i) y 51bis 1(a)8i) Nombre: Esta aclaración se hace con el propósito de:	En relación con esta solicitud internacional Franke, Patrick of McNair-Promenade 124 D-14167 Berlin Alemania El inventor de la material objeto para la cual se busca protección por medio de esta solicitud internacional Todos los designados

IX	Lista verificada	Número de hojas	
IX-1	Solicitud	5	-
IX-2	Descripción	25	-
IX-3	Reivindicaciones	5	-
IX-4	Resumen	1	EZABSTOO.TXT
IX-5	Dibujos	0	
IX-7	TOTAL	36	

	Articulos anexos	Documento (os) anexos	Archivos (os) Electrónicos
IX-8	Hoja de cálculo de derecho	✓	-
IX-11	Copia del poder general del apoderado	Referencia No. 42894	
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figura de los dibujos que deben ser unidos al resumen		
IX-20	Idioma de presentación de la solicitud internacional		Inglés
X-1	firma del solicitante o agente		(firma)
X-1-1	nombre		DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN
X-1-2	Nombre del signatario		Sandra Pohlman
X-1-3	Puesto		Agente legal (Inglaterra y Gales), Practicante No. 157080

PARA USO UNICAMENTE DE LA OFICINA RECEPTORA		
10-1	Fecha de recepción de la Solicitud Internacional propuesta	
10-2	Dibujos recibidos	
10-2-1		
10-2-2	no recibidos	
10-3	Fecha corregida de la recepción actual conveniente al último pero inconveniente a los documentos recibidos oportunamente o dibujos que completen la Solicitud Internacional propuesta.	
10-4	Fecha de recepción oportuna de las correcciones requeridas bajo el Artículo 11 (2) PCT.	
10-5	Autoridad de Búsqueda Internacional	ISA/EP
10-6	Transmisión de la copia buscada retrasada hasta el pago de derecho de la búsqueda	

PARA EL USO UNICAMENTE DE LA OFICINA INTERNACIONAL		
11-1	Fecha y recepción de la copia registrada por la Oficina internacional	

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/EP01/14825

A. CLASIFICACION DE LA MATERIA OBJETO:		
IPC 7 A61K7/48 De acuerdo con la Clasificación de Patente internacional (IPC) o con ambas, la clasificación nacional y la IPC.		
B. CAMPOS BUSCADOS.		
Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación). IPC 7 A61K		
Documentación buscada diferente a la documentación mínima al grado que tales documentos están comprendidos en los campos buscados.		
Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, cuando es práctico, términos usados en la búsqueda). EPO-Internal, CHEM ABS Data		
C. DOCUMENTOS CONSIDERADOS POR SER RELEVANTES.		
Categoría *	Cita de documentos, con indicación, donde es apropiado, de los pasajes relevantes.	Relevante a la reivindicación No
A	DE 198 876 A (COGNIS DEUTSCHLAND GMBH) 13 abril 2000 (2000-04-13) tabla 1 -----	1-17
A	EP 0 847 750 A (BEIERSDORF AG) 17 junio 1998 (1998-06-17) ejemplos 1-16 -----	1-17
A	ANOM.: "Final Report on the safety Assessment of Cetearyl Octanoate" J. AMERICAN COLLEGE OF TOXICOLOGY, vol. 1, no. 4, 1982, páginas 81-90, XP000982324 el documento completo -----	1-17
☐ Documentos adicionales están listados en la continuación del recuadro C. ☒ Los miembros de la familia de patentes se enlistan en el anexo		
* Categorías especiales de documentos citados: "A" Documento que define el estado general de la técnica que no se considera por ser relevancia particular. "E" Documentos anteriores pero publicados en o después de la fecha de presentación internacional. "L" Documento que puede arrojar dudas sobre la o las reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica). "O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio. "P" Documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.		"T" Ultimo documento publicado después de la fecha de presentación internacional o la fecha de prioridad y no estando en conflicto con la solicitud pero citada para entender el principio o teoría que subyace la invención. "X" Documento de relevancia particular; la invención reivindicada no se puede considerar novedosa o no se puede considerar que involucre una etapa inventiva cuando el documento se toma solo. "Y" Documento de relevancia particular; la invención reivindicada no se puede considerar que involucre una etapa inventiva cuando el documento se combina con uno u otro documento más, dicha combinación siendo obvia para una persona experta en la técnica. "&" Documento miembro de la misma familia de patentes.
Fecha de la terminación real de la búsqueda internacional 8 abril 2002		Fecha de depósito en el correo del reporte de búsqueda internacional : 16/04/2002
Nombre y dirección postal de la ISA Oficina Europea de Patentes P.B.5818 Patentlaan 2 (SELLO) NL-2280 HV Rijswijk Pays Bas Tel.:(+31-70) 340-2040, Tx 31 651 epo nl. Fax: (+ 31-70) 340-3016		Funcionario autorizado : Sierra Gonzalez, M

REPORTE DE BUSQUEDA INTERNACIONAL
 Información de los miembros de familia de patentes

Solicitud Internacional No.
 PCT/EP01/14825

Documento de Patente citado en el informe de búsqueda	Fecha de publicación	Miembros de la familia de patentes	Fecha de publicación
DE 19843876 A	13-04-2000	DE 19843876 A1 AU 6084499 A WO 0018357 A1 EP 1115365 A1	13-04-2000 17-04-2000 06-04-2000 18-07-2001
EP 0847750 A	17-06-1998	DE 19651478 A1 EP 0847750 A2 JP 10175839 A	18-06-1998 17-06-1998 30-06-1998

TRATADO DE COOPERACION DE PATENTE

Remitente :

Autoridad Internacional de Examen Preliminar

A:

DF-MP DÖRRIES FRANK-MOLNIA &
POHLMAN
Triftstr. 13
D-80538 München
ALEMANIA

PCT

NOTIFICACION DE LA TRANSMISION DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL (Regla 71.1 del PCT)

Fecha de envío: (día, mes, año)

19/08/2002

Referencia del Solicitante o Agente
SCH10130PCT

NOTIFICACION IMPORTANTE

Solicitud Internacional No.
PCT/EP01/14825

Fecha de presentación internacional (día/mes/año)
14/12/2001

Fecha de prioridad (día/mes/año)
15/12/2000

Solicitante:

SCHERING AG

1.- El solicitante ha sido notificado por este medio que esta Autoridad Internacional de Exámenes Preliminares transmite adjunto el Reporte del Examen Preliminar Internacional y sus anexos, si fuera necesario, establecido en la solicitud internacional.

2.- Una copia del reporte y sus anexos, si fueran necesarios, están siendo transmitidos a la Oficina Internacional para la comunicación de todas las oficinas elegidas.

3.- Donde sea requerido por cualquiera de las oficinas elegidas, la Oficina Internacional preparará un reporte en idioma Inglés (pero no preparará ninguno de los anexos) y transmitirá dicho reporte a esa oficina.

4.- RECORDATORIO

El solicitante deberá entrar antes en la fase nacional de cada oficina elegida para realizar ciertos procedimientos (presentación de traducciones y pago de impuestos nacionales) dentro de los 30 meses a partir de la fecha de prioridad (o después en algunas oficinas) (Artículo 39(1)) (ver también el recordatorio emitido por la Oficina Internacional con la Forma PCT/IB/301).

Donde una traducción de la solicitud internacional haya sido enviada a alguna oficina elegida, la traducción deberá contener una traducción de alguno de los anexos del reporte del examen preliminar internacional. Esta es responsabilidad del solicitante el preparar y enviar cualquier traducción directamente a cada oficina elegida que le concierne.

Para mayores detalles de los limites del tiempo aplicable y requerimientos de las oficinas elegidas, ver el volumen II de la Guía de Solicitudes del PCT.

Para propósitos de decidir si la invención reclamada es patentable o no, las Oficinas electas pueden aplicar criterio adicional o diferente del criterio en el cual ésta basado el reporte del examen preliminar internacional (véase artículo 27 (5), 33(5)) el criterio adicional puede incluir, por ejemplo prerrogativas de patentabilidad y los requerimientos permiten la descripción y claridad y soporte de las reivindicaciones

Nombre y dirección postal de la IPEA/

SELLO

Oficina Europea De Patentes
D-80298 Munich
Tel: (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Funcionario autorizado :

CARDENAS C E

(SELLO)

Tel: (+49-89) 2399-2828

I. Bases Del Reporte

Las bases del reporte de examen preliminar internacional es la solicitud como se presentó originalmente.

V. Testimonio razonado bajo la Regla 66.2(a)(ii) con respecto a la novedad, etapa inventiva o aplicabilidad industrial

En vista de los documentos citados en el reporte de búsqueda internacional, se considera que la invención como se define en las reivindicaciones cumple el criterio mencionados en el artículo 33(1) PCT, es decir, parece ser novedoso, involucra una etapa inventiva y es industrialmente aplicable

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ~~MODELO DE UTILIDAD~~	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO

Radicación : 03050565 00000000 Folios: 100
 Fecha (AND): 2003-06-13 16:56:10
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES