**(12) STANDARD PATENT** (11) Application No. **AU 2007344298 B2**
**(19) AUSTRALIAN PATENT OFFICE**

(54) Title
**Cream-gel comprising at least one retinoid and benzoyl peroxide**

(51) International Patent Classification(s)
***A61Q 19/08*** (2006.01) ***A61K 31/327*** (2006.01)
***A61K 8/04*** (2006.01) ***A61P 17/00*** (2006.01)
***A61K 8/36*** (2006.01) ***A61Q 7/00*** (2006.01)
***A61K 8/38*** (2006.01) ***A61Q 17/04*** (2006.01)
***A61K 31/185*** (2006.01) ***A61Q 19/00*** (2006.01)

(21) Application No: **2007344298** (22) Date of Filing: **2007.12.21**

(87) WIPO No: **WO08/087354**

(30) Priority Data

| (31) Number | (32) Date | (33) Country |
|---|---|---|
| **0655784** | **2006.12.21** | **FR** |

(43) Publication Date: **2008.07.24**
(44) Accepted Journal Date: **2013.07.11**

(71) Applicant(s)
**GALDERMA RESEARCH & DEVELOPMENT**

(72) Inventor(s)
**Mallard, Claire;At, Emmanuelle;Louis, Fabienne**

(74) Agent / Attorney
**Griffith Hack, GPO Box 1285, Melbourne, VIC, 3001**

(56) Related Art
**FR 2687312 A1**
**Martin, B et al (1998) British Journal of Dermatology 139: 8-11**
**WO2003/055472A1**
**US 2003/0170196 A1***

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau international

(43) Date de la publication internationale
24 juillet 2008 (24.07.2008)

PCT

(10) Numéro de publication internationale
WO 2008/087354 A3

(51) Classification internationale des brevets :
*A61Q 19/08* (2006.01) *A61K 8/38* (2006.01)
*A61Q 7/00* (2006.01) *A61K 31/327* (2006.01)
*A61Q 17/04* (2006.01) *A61P 17/00* (2006.01)
*A61Q 19/00* (2006.01) *A61K 31/185* (2006.01)
*A61K 8/36* (2006.01) *A61K 8/04* (2006.01)

(21) Numéro de la demande internationale :
PCT/FR2007/052613

(22) Date de dépôt international :
21 décembre 2007 (21.12.2007)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
0655784 21 décembre 2006 (21.12.2006) FR

(71) Déposant *(pour tous les États désignés sauf US)* : **GALDERMA RESEARCH & DEVELOPMENT** [FR/FR]; 2400 Route des Colles, Les Templiers, F-06410 Biot (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants *(pour US seulement)* : **MALLARD, Claire** [FR/FR]; Domaine La Jouvencelle, 1122 Chemins du Château, F-06250 Mougins (FR). **LOUIS, Fabienne** [FR/FR]; 17, avenue du Loup, Immeuble l'Arizona, F-06270 Villeneuve-Loubet (FR). **AT, Emmanuelle** [FR/FR]; Résidence la Baie des Combes, 378 chemin des Combes, F-06600 Antibes (FR).

(74) Mandataire : **ANDRAL, Christophe**; L'Oreal, RIVER PLAZA - DIPI, 25-29 Quai Aulagnier, F-92665 Asnieres-Sur-Seine (FR).

(81) États désignés *(sauf indication contraire, pour tout titre de protection nationale disponible)* : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) États désignés *(sauf indication contraire, pour tout titre de protection régionale disponible)* : ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publiée :
— *avec rapport de recherche internationale*
— *avant l'expiration du délai prévu pour la modification des revendications, sera republiée si des modifications sont reçues*

(88) Date de publication du rapport de recherche internationale: 13 novembre 2008

(54) Title: CREAM-GEL COMPRISING AT LEAST ONE RETINOID AND BENZOYL PEROXIDE

(54) Titre : GEL CREME COMPRENANT AU MOINS UN RETINOIDE ET DU PÉROXYDE DE BENZOYLE

(57) Abstract: The invention relates to a composition in the form of a cream-gel comprising, in a physiologically acceptable medium, at least one retinoid and dispersed benzoyl peroxide, to the method for the preparation thereof and to the cosmetic and dermatological use thereof.

(57) Abrégé : L'invention se rapporte à une composition sous forme de gel-crème comprenant, dans un milieu physiologiquement acceptable, au moins un rétinoïde, et du peroxyde de benzoyle dispersé, à son procédé de préparation et à son utilisation en cosmétique et en dermatologie.

WO 2008/087354 A3

# CREAM GEL COMPRISING AT LEAST ONE RETINOID AND BENZOYL PEROXIDE

The invention relates to a composition in the form of a cream gel comprising, in a physiologically acceptable medium, at least one dispersed retinoid and dispersed benzoyl peroxide.

The use of several categories of active principles is a therapeutic tool to which recourse is frequently had, in particular in the treatment of dermatological disorders.

Specifically, different antifungals, such as allylamine derivatives, triazoles, antibacterials or antimicrobials, such as, for example, antibiotics, quinolones and imidazoles are conventionally combined in the treatment of dermatological diseases. It is also known to use peroxides, vitamins D and retinoids in the topical treatment of various pathologies related to the skin or mucous membranes, in particular acne.

The combination of several local treatments (antibiotics, retinoids, peroxides, zinc) is also used in dermatology in order to make it possible to enhance the effectiveness of the active principles and to reduce their toxicity (Cunliffe W.J., *J. Dermatol. Treat.*, 2000, 11 (suppl.2), S13-S14).

The multiple application of different dermatological products may be fairly burdensome and demanding for the patient.

The interest in attempting to obtain a novel treatment which is effective with regard to dermatological conditions in a stable composition which offers a good cosmetic quality, which makes possible a single application and which makes possible a use which is agreeable to the patient is thus understood.

There is nothing among this range of therapies provided to a person skilled in the art which would encourage him to combine, in the same composition, benzoyl peroxide and a retinoid.

However, the formulation of such a composition

presents several problems.

First of all, the effectiveness of the benzoyl peroxide is related to its decomposition when it is brought into contact with the skin. This is because it is the oxidizing properties of the free radicals produced during this decomposition which result in the desired effect. Consequently, in order for the benzoyl peroxide to maintain an optimum effectiveness, it is important to prevent it from decomposing before use, that is to say during storage.

In point of fact, benzoyl peroxide is an unstable chemical compound, which makes it difficult to formulate it in finished products.

The solubility and the stability of benzoyl peroxide have been studied by Chellquist et al. in ethanol, propylene glycol and various mixtures of polyethylene glycol 400 (PEG 400) and water (Chellquist E.M. and Gorman W.G., *Pharm Res.*, 1992, Vol. 9, 1341-1346).

Benzoyl peroxide is particularly soluble in PEG 400 and ethanol, as is shown in the following table:

| **Solvent** | **Solubility of benzoyl peroxide (mg/g)** |
|---|---|
| PEG 400 | 39.6 |
| Ethanol | 17.9 |
| Propylene glycol | 2.95 |
| Propylene glycol/water (75:25) | 0.36 |
| Glycerol | 0.15 |
| Water | 0.000155 |

This document furthermore specifies that the stability of benzoyl peroxide is strongly influenced by the chemical composition of the formulation and by the storage temperature. Benzoyl peroxide is highly reactive and decomposes in solution at low temperature due to the instability of its peroxide bond.

The authors thus find that benzoyl peroxide in solution decomposes more or less rapidly in all the solvents

studied according to the type of solvent and its concentration.

The decomposition times of benzoyl peroxide in PEG 400 (0.5 mg/g), in ethanol and in propylene glycol are 1.4, 29 and 53 days respectively at 40°C.

Such a decomposition does not make possible the preparation of a product intended for sale.

Furthermore, it is known that benzoyl peroxide is more stable in water and propylene glycol when it is in suspension (i.e., in the dispersed form), since it is not decomposed after storing for 90 days in these solvents.

Thus, in order to limit the problem of rapid instability of benzoyl peroxide in solution, it has proven to be advantageous to formulate benzoyl peroxide in the dispersed form. However, this type of formulation is not completely satisfactory insofar as the benzoyl peroxide is still found to be decomposed in the finished product.

Another difficulty to be overcome in the preparation of a composition comprising both benzoyl peroxide and a retinoid is that the majority of retinoids are particularly sensitive to natural oxidation, to visible light and ultraviolet radiation and, as benzoyl peroxide is a strong oxidizing agent, the chemical compatibility of these compounds in one and the same formulation presents numerous problems of stability from the physical and chemical viewpoint.

A stability study was carried out on two retinoids by combining two commercial products, one comprising a retinoid (tretinoin or adapalene) and the second based on benzoyl peroxide (*B. Martin et al., Br. J. Dermatol., (1998) 139, (suppl. 52), 8-11).*

The presence of the formulation based on benzoyl peroxide causes very rapid decomposition of the oxidation-sensitive retinoids: 50% of the tretinoin is measured as decomposing in 2 hours and 95% in 4 hours. In the composition in which the retinoid is adapalene, no decomposition of the adapalene was measured during

24 hours. This study confirms that benzoyl peroxide is decomposed and decomposes oxidation-sensitive retinoids over time by gradually releasing benzoic acid in finished products.

In point of fact, it is clear that the decomposition of benzoyl peroxide and retinoids is not desirable insofar as it is harmful to the effectiveness of the composition in which they are present.

Nothing prompted the combining of these two active agents in order to obtain a stable composition of emulsion type, it being known that it was conventionally recognized that the presence of benzoyl peroxide chemically and physically destabilized this type of composition.

The formulation as a cream gel of benzoyl peroxide and a retinoid can be advantageous for topical treatments, such as that of acne, as, while contributing emollience, it avoids in particular leaving an excessively greasy feel remaining on the skin.

In point of fact, another difficulty to be overcome in the preparation of such a composition comprising in particular dispersed active principles, such as adapalene and benzoyl peroxide, is the sedimentation of the active principles. This is because, while the "light" feel of such a formulation is related to the fact that the external phase is aqueous, it also depends on its composition and in particular on the presence of thickeners. In point of fact, in cream gels, the thickeners for the fatty phase, such as waxes and solid fatty alcohols and esters, are greatly reduced, to the advantage of gelling agents for the aqueous phase. However, the majority of gelling agents for the aqueous phase are destabilized by the benzoic acid which is released during the decomposition of the benzoyl peroxide.

Specifically, the thickening agents most commonly used for the formulation of gels with benzoyl peroxide are acrylic acid polymers (Carbomer) and celluloses, alone

2007344298 07 Jun 2013

or in combination with silicates.

In point of fact, the use of carbomers in compositions of aqueous gel type does not give good results in terms of chemical stability of the benzoyl peroxide and in terms of rheological stability. As described by Bollinger (Bollinger, Journal of Pharmaceutical Science, 1977, vol. 5), a loss of 5 to 20% of benzoyl peroxide after 2 months at 40°C, depending on the neutralizing agent of the carbomer used, was observed. Furthermore, the release of benzoic acid brings about depolymerization of the carbomers, giving a fall in viscosity which may bring about phase separation.

In other gels composed of a mixture of hydroxypropylcellulose and of magnesium aluminium silicate, a fall in viscosity over time is also observed and results in sedimentation of the suspended active principles and in the dispersion in the finished product being heterogeneous.

This instability of benzoyl peroxide gels is harmful to their effectiveness and to their cosmetic quality and it is highly probable that it is reencountered in cream gels. A finished product, in particular when it concerns pharmaceutical or cosmetic compositions, must maintain, throughout its lifetime, precise physicochemical criteria which make it possible to guarantee its pharmaceutical or cosmetic quality respectively. Among these criteria, it is necessary for the rheological properties to be retained. They define the behaviour and the texture of the composition during application but also the properties of release of the active principle [SFSTP Commission report 1998] and the homogeneity of the product when the active principles are present therein in the dispersed state.

The need thus exists to have available a physically and chemically stable cream gel comprising benzoyl peroxide and a retinoid.

In point of fact, the Applicant Company has produced a composition which meets this need. Such a composition is a cream gel as described

2007344298 07 Jun 2013

In one aspect, there is provided a composition comprising a physiologically acceptable medium, dispersed adapalene and dispersed benzoyl peroxide, and at least one lipophilic compound making up a fatty phase, and wherein the composition is devoid of any emulsifying agent.

In another aspect, there is provided a composition in the form of a cream gel comprising:

- dispersed benzoyl peroxide, in particular in the free or encapsulated form,
- at least one retinoid being adapalene,
- at least one lipophilic compound making up the fatty phase, and
- at least one pH-independent gelling agent which has good physical stability, that is to say which does not exhibit a fall in viscosity over time and at temperatures of between 4°C and 40°C, and which maintains good chemical stability for the two active principles (benzoyl peroxide and retinoid), that is to say that decomposition of active principles over time and at temperatures between 4°C and 40°C is not observed.

The compositions of the present invention can be provided in all the formulation forms normally used for topical application and in particular in the form of a cream gel with a semiliquid consistency of the milk type or with a solid consistency of the cream type obtained by dispersion of a fatty phase in an aqueous phase (O/W).

A person skilled in the art will take care to choose the excipients constituting the compositions according to the invention as a function of the consistency desired and so that the advantageous properties of the composition according to the invention are respected.

The composition according to the invention can in particular comprise, in addition to at least one retinoid, benzoyl peroxide, a fatty phase and at least one pH-independent gelling agent, one or more of the following ingredients:

2007344298 07 Jun 2013

following ingredients:

a) one or more wetting agents,

b) one or more chelating agents,

c) an aqueous phase,

d) one or more additives.

The Applicant Company has also discovered, surprisingly, that it is possible to obtain an advantageous homogeneous dispersion of active principles by following a specific preparation process. This preparation process makes it possible to obtain an optimum particle size and a homogeneous dispersion of the two active principles in the composition while guaranteeing the physical stability of the product.

The invention thus relates to a composition in the form of a cream gel comprising, in a physiologically acceptable medium, at least one dispersed retinoid being adapalene and dispersed benzoyl peroxide.

The composition according to the invention is preferably in the form of an aqueous cream gel.

The cream gel is characterized by the presence of gelling agents for the aqueous phase and of a fatty phase. On the other hand, there is (are) no emulsifier(s) which differentiates cream gels from emulsions.

The term "emulsifiers" is understood to mean amphiphilic compounds which have a hydrophobic part having an affinity for the oil and a hydrophilic part having an affinity for the water, thus creating a connection between the two phases. Ionic or nonionic emulsifiers thus stabilize O/W emulsions by being adsorbed at the interface and by forming lamellar layers of liquid crystals.

In particular, the composition according to the invention is physically and chemically stable.

The term "physiologically acceptable medium" is understood to mean a medium compatible with topical application on the skin, superficial body growths and/or mucous membranes.

The composition according to the invention

2007344298 07 Jun 2013

comprises at least one retinoid. The term "retinoid" is understood to mean any compound which binds to RAR and/or RXR receptors.

Mention may be made, by way of example, as retinoid, of retinoic acid, tretinoin, tazarotene and those described in the following patents or patent applications:

US 4,666,941, US 4,581,380, EP 0 210 929, EP 0 232 199, EP 0 260 162, EP 0 292 348, EP 0 325 540, EP 0 359 621,

EP 0 409 728, EP 0 409 740, EP 0 552 282, EP 0 584 191, EP 0 514 264, EP 0 514 269, EP 0 661 260, EP 0 661 258, EP 0 658 553, EP 0 679 628, EP 0 679 631, EP 0 679 630, EP 0 708 100, EP 0 709 382, EP 0 722 928, EP 0 728 739, EP 0 732 328, EP 0 749 937, EP 0 776 885, EP 0 776 881, EP 0 823 903, EP 0 832 057, EP 0 832 081, EP 0 816 352, EP 0 826 657, EP 0 874 626, EP 0 934 295, EP 0 915 823, EP 0 882 033, EP 0 850 909, EP 0 879 814, EP 0 952 974, EP 0 905 118, EP 0 947 496, WO98/56783, WO99/10322, WO99/50239, WO99/65872.

Due to their ability to bind RAR and/or RXR receptors, the compounds resulting from the family of the benzonaphthalene retinoids, such as described in Patent Application EP 0 199 636, are also included in the invention.

Preferably, the naphthoic acid derivatives will be chosen and in particular:

6-(3-methylphenyl)-2-naphthoic acid and its methyl ester,

6-(4-(tert-butyl)phenyl)-2-naphthoic acid and its methyl ester,

6-(3-(tert-butyl)phenyl)-2-naphthoic acid and its methyl ester,

6-(3,4-dimethoxyphenyl)-2-naphthoic acid and its methyl ester,

6-(p-(1-adamantylthio)phenyl)-2-naphthoic acid and its methyl ester,

6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid (adapalene) and its methyl ester,

the methyl ester of 6-[3-(1-adamantyl)-4-(tert-butyl-dimethylsilyloxy)phenyl]-2-naphthoic acid,

the methyl ester of 6-[3-(1-adamantyl)-4-hydroxy-phenyl]-2-naphthoic acid,

6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid,

the methyl ester of 6-[3-(1-adamantyl)-4-decyloxy-phenyl]-2-naphthoic acid,

6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

the methyl ester of 6-[3-(1-adamantyl)-4-hexyloxy-phenyl]-2-naphthoic acid,

6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,
the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-acetoxy-1-methyl-2-naphthoic acid,
6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid,
the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid,
the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid,
6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid,
6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthalenemethanol,
the ethyl amide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,
the morpholide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,
the methyl ester of 6-[3-(tert-butyl)-4-methoxyphenyl]-2-naphthoic acid,
6-[3-(tert-butyl)-4-methoxyphenyl]-2-naphthoic acid,
the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid,
6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid.

In particular, preference will be given to adapalene and its salts.

The term "salts of adapalene" is understood to mean the salts formed with a pharmaceutically acceptable base, in particular inorganic bases, such as sodium hydroxide, potassium hydroxide and ammonia, or organic bases, such as lysine, arginine or N-methylglucamine.

The term "salts of adapalene" is also understood to mean the salts formed with fatty amines, such as dioctylamine and stearylamine.

Of course, the amount of the two active agents, benzoyl peroxide and retinoid, in the composition according to the invention will depend on the combination chosen and thus particularly on the retinoid under consideration and on the quality of the

treatment desired.

The preferred retinoid concentrations are between 0.0001 and 20% by weight, with respect to the total weight of the composition.

Preferably, in the case of adapalene, the composition according to the invention comprises between 0.001 and 5% by weight and advantageously between 0.01 and 1% by weight of adapalene, with respect to the total weight of the composition, preferentially between 0.01 and 0.5% by weight, preferably between 0.1 and 0.4% by weight of adapalene, more preferably still 0.3% by weight of adapalene.

The benzoyl peroxide can just as easily be used in the free form or else in an encapsulated form, for example in a form adsorbed on or absorbed in any porous support. It can, for example, be benzoyl peroxide encapsulated in a polymeric system composed of porous microspheres, such as, for example, microsponges sold under the name of Microsponges P009A Benzoyl Peroxide by Amcol.

To give an order of magnitude, the composition according to the invention advantageously comprises between 0.0001 and 20% by weight of benzoyl peroxide and between 0.0001 and 20% by weight of retinoid, with respect to the total weight of the composition, and preferably between 0.025 and 10% by weight of benzoyl peroxide and between 0.001 and 10% by weight of retinoid respectively, with respect to the total weight of the composition.

For example, in the compositions for the treatment of acne, the benzoyl peroxide is preferably used at concentrations ranging from 2 to 10% by weight and more particularly from 2.5 to 5% by weight, with respect to the total weight of the composition. The retinoid for its part is used in this type of composition at concentrations generally ranging from 0.01 to 1% by weight, with respect to the total weight of the composition.

Advantageously, the particle size of the retinoid

and of the benzoyl peroxide is such that at least 80% by number of the particles and preferably at least 90% by number of the particles have a diameter of less than 25 μm and at least 99% by number of the particles have a diameter of less than 100 μm.

Preferably, the cream gel according to the invention comprises one or more gelling agents and/or suspending agents and/or pH-independent gelling agents. The term "pH-independent gelling agent" is understood to mean a gelling agent capable of conferring a viscosity on the composition sufficient to keep the retinoid and the benzoyl peroxide in suspension, even under the influence of a variation in pH due to the release of benzoic acid by the benzoyl peroxide.

Mention may be made, as nonlimiting examples of gelling agents and/or suspending agents and/or pH-independent gelling agents which can participate in the compositions according to the invention, of the acrylates/$C_{10-30}$ alkyl acrylate crosspolymer sold under the name of Pemulen TR-1 or Pemulen TR-2 by Noveon, "electrolyte-insensitive" carbomers, sold under the name of Ultrez 20®, Carbopol 1382 or Carbopol ETD2020NF® by Noveon, polysaccharides, with, as nonlimiting examples, xanthan gum, such as the Xantural 180®, sold by Kelco, guar gum, chitosans, carrageenans, in particular divided into four main families: κ, λ, β and ω, such as the Viscarin® products and Gelcarin® products sold by IMCD, cellulose and its derivatives, such as hydroxypropylmethylcellulose, in particular the product sold under the name of Methocel E4 Premium by Dow Chemical, or hydroxyethylcellulose, in particular the product sold under the name of Natrosol HHX 250® by Aqualon, or also the product "microcrystalline cellulose and carboxymethyl cellulose sodium" sold under the name of Avicel CL-611 by FMC Biopolymer, the family of magnesium aluminium silicates, such as Veegum K, sold by Vanderbilt, the family of acrylic polymers coupled to hydrophobic chains, such as the PEG-150/decyl/SMDI copolymer sold under the name of

Aculyn 44 (polycondensate comprising at least, as components, a polyethylene glycol comprising 150 or 180 mol of ethylene oxide, decyl alcohol and methylene-bis(4-cyclohexyl isocyanate) (SMDI), at 35% by weight in a mixture of propylene glycol (39%) and water (26%)), the family of modified starches, such as the modified potato starch sold under the name of Structure Solanace, and also their mixtures, and gelling agents of the family of polyacrylamides, such as the sodium acryloyldimethyltaurate copolymer/isohexadecane/polysorbate 80 mixture sold under the name Simulgel 600PHA by Seppic or the polyacrylamide/C13-14 isoparaffin/laureth-7 mixture, such as, for example, that sold under the name of Sepigel 305 by Seppic.

The preferred gelling agents result from the family of polyacrylamides, such as Simulgel 600PHA or Sepigel 305; "electrolyte-insensitive" carbomers, such as Carbopol ETD2020 NF; polysaccharides, such as xanthan gum; cellulose derivatives, such as hydroxypropylmethylcellulose or hydroxyethylcellulose; or magnesium aluminium silicates, alone or as a mixture.

The gelling agent or suspending agent as described above can be used at the preferred concentrations ranging from 0.001 to 15% and more preferably ranging from 0.1 to 5%.

Mention may be made, among chelating agents, as nonlimiting examples, of ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), ethylenediaminedi(o-hydroxyphenylacetic acid) (EDDHA), (2-hydroxyethyl)ethylenediaminetriacetic acid (HEDTA), ethylenediaminedi(o-hydroxy-p-methylphenylacetic acid) (EDDHMA) and ethylenediaminedi(5-carboxy-2-hydroxyphenylacetic acid) (EDDCHA).

Mention may be made, as preferred chelating agent, of ethylenediaminetetraacetic acid (EDTA).

The concentrations of chelating agent can vary from 0% to 1.5% by weight, preferably from 0.05% to 0.5% by weight, with respect to the total weight of the composition.

The compositions of the invention can comprise one or more wetting agents at concentrations of 0 to 20% by weight, preferably of 0 to 10% by weight, with respect to the total weight of the composition. When these ingredients are present in the composition, they are at concentrations ranging from 0.001 to 20% by weight, preferentially from 0.1% to 10% by weight, preferably from 0.1% to 7% by weight and more preferably still from 2 to 7% by weight, with respect to the total weight of the composition. They should not dissolve the active principles at the percentage used, should not cause exothermic reactions harmful to the benzoyl peroxide, should help in dispersing the active principles well and should have antifoaming properties. The wetting power is the tendency of a liquid to spread out over a surface.

Preferably, the wetting agents are ones which can exhibit an HLB (Hydrophilic-Lipophilic Balance) of 7 to 16. Mention will be made, as nonlimiting examples, of the Poloxamers and more particularly Synperonic PE/L44 and/or Synperonic PE/L62, sold by Uniqema, glycols, such as propylene glycol, dipropylene glycol, propylene glycol dipelargonate, lauroglycol or ethoxydiglycol, sorbitan esters, such as POE (20) sorbitan monooleate, sold under the name of Tween 80 by Uniqema, and POE (20) sorbitan monostearate, sold under the name of "Tween 60" by Uniqema, ethers of fatty alcohols, such as Ceteareth-20, sold under the name of Eumulgin B2 by Cognis, glycerol esters, such as glycerol monostearate, sold under the name of "Cutina GMS" by Cognis, polyoxyethylene (21) stearyl ether, sold under the name of Brij 721 by Uniqema, methyl glucose sesquistearate, sold under the name of Glucate SS by Noveon, or PEG-20 methyl glucose sesquistearate, sold under the name of Glucamate SSE-20 by Noveon.

Use is preferably made, among wetting agents, of wetting agents which can preferably exhibit an HLB of 10 to 14, without this list being limiting, of compounds of the family of the Poloxamers and more

particularly Synperonic PE/L44 and/or Synperonic PE/L62 or of glycols, such as propylene glycol, dipropylene glycol, propylene glycol dipelargonate, lauroglycol or ethoxydiglycol.

The particularly preferred wetting agents are propylene glycol or Synperonic PE/L44 (polyethylene-polypropylene glycol; polyoxyethylene-polyoxypropylene block copolymer).

According to the invention, the cream gel comprising the benzoyl peroxide and a retinoid advantageously comprises at least water and at least one gelling agent and/or suspending agent and/or pH-independent gelling agent and can also comprise one or more wetting agents.

The composition according to the invention also comprises a fatty phase. This fatty phase can comprise lipophilic compounds, alone or as a mixture, such as, for example, vegetable, mineral, animal or synthetic oils, silicone oils and their mixtures.

Mention may be made, as example of mineral oil, for example, of liquid paraffins with different viscosities, such as Primol 352®, Marcol 82® or Marcol 152®, sold by Esso.

Mention may be made, as vegetable oil, of sweet almond oil, palm oil, soybean oil, sesame oil or sunflower oil.

Mention may be made, as animal oil, of lanolin, squalene, fish oil or mink oil, with, as derivative, the squalane sold under the name Cosbiol® by Laserson.

Mention may be made, as synthetic oil, of an ester, such as cetearyl isononanoate, for example the product sold under the name of Cetiol SN PH® by Cognis France, isopropyl palmitate, for example the product sold under the name of Crodamol IPP® by Croda, diisopropyl adipate, sold under the name of Crodamol DA by Croda, or caprylic/capric triglyceride, such as Miglyol 812®, sold by Hüls/Univar.

Mention may be made, as volatile or nonvolatile silicone oil, of dimethicones, such as the products

sold under the name of Q7-9120 Silicone Fluid with a viscosity of between 20 cSt and 12 500 cSt or the product sold under the name ST-Cyclomethicone-5 NF® by Dow Corning.

It will also be possible to put solid fatty substances, such as natural or synthetic waxes. In this case, a person skilled in the art will adjust the heating temperature of the preparation according to the presence or absence of these solids.

For the composition according to the invention, synthetic oils and silicone oils and more particularly Marcol 152® and ST-Cyclomethicone 5 NF® are preferred.

The aqueous phase of the cream gel according to the invention can comprise water. This water can in particular be a floral water, such as cornflower water, or a natural thermal or mineral water, for example chosen from water from Vittel, waters from the Vichy basin, water from Uriage, water from La Roche-Posay, water from Avène or water from Aix-les-Bains.

The said aqueous phase can be present at a content of between 10 and 90% by weight, with respect to the total weight of the composition, preferably between 20 and 80% by weight.

The composition can additionally comprise any additive conventionally used in the cosmetics or pharmaceutical field, such as a stabilizing agent for benzoyl peroxide (by way of example, sodium docusate or sodium $C_{14-16}$ olefinsulphonate), neutralizing agents of normal inorganic or organic base or acid type (by way of example, triethanolamine, 10% sodium hydroxide solution, the citric acid/sodium citrate buffer or the succinic acid/sodium succinate buffer), antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants and/or emollients, colorants, fragrances, essential oils, cosmetic active principles, moisturizing agents, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, such as DHA, soothing agents and protective agents for the skin, such as allantoin. Of course, a person skilled in the

art will take care to choose this or these optional additional compounds and/or their amounts in such a way that the advantageous properties of the composition according to the invention are not, or not substantially, detrimentally affected.

These additives can be present in the composition in a proportion of 0.001 to 20% by weight, with respect to the total weight of the composition.

Mention may be made, as examples of preservatives, of benzalkonium chloride, bronopol, chlorhexidine, chlorocresol and its derivatives, ethyl alcohol, phenethyl alcohol, phenoxyethanol, potassium sorbate, diazolidinylurea, benzyl alcohol, parabens or their mixtures.

Mention may be made, as examples of humectants and/or emollients, of glycerol and sorbitol, sugars (by way of example, glucose or lactose), PEGs (by way of example, Lutrol E400), urea or amino acids (by way of example, serine, citrulline or alanine).

In particular, the invention also relates to a pharmaceutical or cosmetic composition in the form of a cream gel comprising, in a physiologically acceptable medium compatible with topical application to the skin, superficial body growths or mucous membranes, the ingredients (expressed as percentage by weight) chosen from:

- from 0.001% to 5%, preferably from 0.01% to 0.5%, of a retinoid and preferably of a naphthoic acid derivative;
- from 0.025% to 10%, preferably from 2% to 10%, of benzoyl peroxide;
- from 30% to 95%, preferably from 50% to 85%, of water;
- from 0.01% to 15%, preferably from 0.1% to 5%, of one or more gelling agents and/or suspending agents and/or pH-independent gelling agents;
- from 2% to 50%, preferably from 5% to 30%, of fatty phase;
- from 0% to 1.5%, preferably from 0.05% to 0.5%, of

chelating agents;

- from 0% to 10%, preferably from 2% to 7%, of one or more wetting agents;

- from 0% to 3%, preferably from 0.05% to 1%, of preservatives;

- from 0% to 20%, preferably from 2% to 15%, of humectants and/or emollients;

- from 0% to 3%, preferably from 0.05% to 2%, of stabilizing agents;

- from 0% to 10%, preferably from 0.1% to 5%, of neutralizing agents.

Another subject-matter of the present invention is the composition as described above as medicament.

The invention also relates to the use of the novel composition as described above in cosmetics and in dermatology.

Due to the keratolytic, bactericidal and anti-inflammatory activity of benzoyl peroxide and the marked activity of retinoids in the fields of cell differentiation and proliferation, the compositions of the invention are particularly well suited to the following therapeutic fields:

1) for treating dermatological conditions linked to a disorder of keratinization involving differentiation and proliferation, in particular for treating acne vulgaris, comedonic or polymorphic acne, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acnes, such as solar, drug or occupational acne, or hidradenitis suppurativa,

2) for treating other types of disorders of keratinization, in particular ichthyoses, ichthyosiform conditions, Darier's disease, palmoplantar keratoderma, leucoplakia and leucoplakiform conditions, or cutaneous or mucosal (oral) lichen,

3) for treating other dermatological conditions linked to a disorder of keratinization with an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether cutaneous, mucosal or ungual, and even psoriatic rheumatism, or alternatively

cutaneous atopy, such as eczema, or respiratory atopy or alternatively gingival hypertrophy; the compounds can also be used in some inflammatory conditions not exhibiting disorder of keratinization, such as folliculitis,

4) for treating all dermal or epidermal proliferations, whether they are benign or malignant and whether they are or are not of viral origin, such as common warts, flat warts, molluscum contagiosum and epidermodysplasia verruciformis, florid or oral papillomatoses, and the proliferations which can be induced by ultraviolet radiation, in particular in the case of actinic keratoses,

5) for repairing or combating skin ageing, whether photoinduced or chronologic, or for reducing pigmentations, or any pathology associated with chronologic or actinic ageing;

6) for preventively or curatively treating disorders of cicatrization or skin ulcers, for preventing or repairing stretch marks, or alternatively for promoting cicatrization,

7) for combating disorders of the sebaceous function, such as hyperseborrhoea of acne or simple seborrhoea,

8) in the treatment of any condition of fungal origin on the skin, such as tinea pedis and tinea versicolor,

9) in the treatment of dermatological conditions with an immunological component,

10) in the treatment of skin disorders due to exposure to UV radiation, and

11) in the treatment of dermatological conditions linked to inflammation or infection of the tissues surrounding the hair follicle, in particular due to microbial colonization or infection, in particular impetigo, seborrhoeic dermatitis, folliculitis or sycosis barbae, or involving any other bacterial or fungal agent.

The compositions according to the invention are particularly suited to the preventive or curative treatment of acne vulgaris.

A subject-matter of the invention is also the preparation of a pharmaceutical composition intended for the prevention and/or treatment of dermatological conditions linked to disorders of cell differentiation and/or proliferation and/or of keratinization, preferably acne vulgaris.

The compositions according to the invention also find an application in body and hair hygiene.

The present invention thus also relates to the cosmetic use of a composition according to the invention for the treatment of skin with a tendency towards acne, for causing hair growth or preventing hair loss, for combating the greasy appearance of the skin or hair, in protecting against the harmful effects of the sun or for preventing and/or combating photoinduced or chronologic ageing.

Preferably, the said compositions according to the invention are administered topically.

Another subject-matter of the invention is a process for the preparation of a composition as described above. Such a process is characterized in that it comprises a stage of mixing a physiologically acceptable medium with at least one naphthoic acid derivative and at least benzoyl peroxide.

The other optional excipients and additives will be introduced according to the chemical nature of the compounds and the formulation form chosen.

Generally, the preparation of a composition according to the invention takes place thus according to the following main process:

a) mixing at least one retinoid with water until it has completely dispersed, in order to obtain active phase 1;

b) mixing the benzoyl peroxide with water until it has completely dispersed, in order to obtain active phase 2;

c) mixing at least one gelling agent and/or suspending agent and/or pH-independent gelling agent with water, optionally one or more chelating agents, one or more

preservatives, one or more humectants and/or emollients, one or more stabilizing agents and the hydrophilic additives, in order to obtain the aqueous phase;

d) optionally, mixing at least two lipophilic compounds, in order to obtain the fatty phase;

e) mixing the 2 active phases obtained in a) and b), in order to obtain a single active phase;

f) introducing the single active phase obtained in e) into the aqueous phase obtained in c);

g) introducing the single compound of the fatty phase or optionally the fatty phase obtained in d), in order to obtain a cream gel;

h) if necessary, the heat-sensitive additives are added;

i) if necessary, a neutralizing agent for the gelling agent is introduced into the cream gel obtained in h) or i);

j) if necessary, further water is added.

Generally, the preparation of a composition according to the invention takes place thus according to the following alternative process:

a') Stages a) and b) are combined, so as to obtain stage a'), which corresponds to the mixing of at least one retinoid and benzoyl peroxide with water and at least one wetting agent until they have completely dispersed, in order to obtain the single active phase.

Stages c), d), f), g), h), i) and j) of the main process remain unchanged. As regards step e), this is deleted.

According to a specific embodiment, the preparation of a composition according to the invention takes place, by way of example, according to the following main process:

a) the retinoid, preferably the naphthoic acid derivative, is mixed with at least one wetting agent in water until the said naphthoic acid derivative has completely dispersed, in order to obtain active phase 1;

b) the benzoyl peroxide is mixed with at least one wetting agent in water until it has completely dispersed, in order to obtain active phase 2;

c) one or more gelling agents and/or suspending agents and/or pH-independent gelling agents (with the exception of the polyacrylamide) and optionally one or more chelating agents, one or more preservatives, one or more humectants and/or emollients, one or more stabilizing agents and the heat-insensitive hydrophilic additives are dissolved in the water with stirring, if necessary under hot conditions. Stirring is maintained and optional heating is maintained until homogeneity is achieved, in order to obtain the aqueous phase;

d) optionally, at least oils, and optionally solid fatty substances, and preservatives and the heat-insensitive lipophilic additives are mixed, if necessary under hot conditions, until homogeneity is achieved, in order to obtain the fatty phase;

e) active phases 1 and 2 are mixed, so as to obtain a single active phase;

f) the single active phase obtained in e) is added to the aqueous phase obtained in c);

g) optionally, the polyacrylamide is introduced into the phase obtained in f);

h) the single fatty phase constituent or optionally the said fatty phase obtained in d) is introduced into the phase obtained in f) or g), in order to obtain a cream gel;

i) if necessary, the heat-sensitive additives are added;

j) if necessary, a neutralizing agent for the gelling agent is introduced into the cream gel obtained in f), in order to obtain the desired pH;

k) if necessary, further water is added.

In particular, the preparation of a composition according to the invention takes place thus according to the following alternative process:

a') Stages a) and b) are combined, so as to obtain stage a'), which corresponds to the mixing of at least

one retinoid and benzoyl peroxide with water and at least one wetting agent until they have completely dispersed, in order to obtain the single active phase.

Stages c), d), f), g), h), i), j) and k) of the main process remain unchanged. As regards stage e), it is deleted.

More specifically, by way of example, the main process for the preparation of the composition according to the invention comprises the following stages:

**Stage a:** Preparation of active phase 1:

The active principle (adapalene), a portion of the purified water and the wetting agent or agents (propylene glycol, Synperonic PE/L62, Synperonic PE/L44 type) are weighed in a beaker. They are dispersed with stirring until they have completely dispersed.

**Stage b:** Preparation of active phase 2:

The active principle (benzoyl peroxide), a portion of the purified water and the wetting agent or agents (propylene glycol, Synperonic PE/L62, Synperonic PE/L44 type) are weighed in a beaker. They are dispersed with stirring until they have completely dispersed.

**Stage c:** Preparation of the aqueous phase:

The remaining purified water, the gelling agent or agents (Carbopol, Pemulen TR1, Xantural, Methocel type) and/or suspending agent or agents (Avicel CL-611 type) and/or pH-independent gelling agent or agents (with the exception of Simulgel 600PHA) and optionally one or more chelating agents (EDTA type), one or more humectants and/or emollients (glycerol type), one or more stabilizing agents (sodium docusate type), one or more preservatives (methylparaben type) and the heat-insensitive hydrophilic additives are introduced with stirring into a beaker, if necessary under hot conditions. Stirring is maintained and optional heating is maintained until the mixture is completely homogeneous.

**Stage d:** Preparation of the fatty phase (optional):

The oily compounds (Olepal isostearique, Cetiol

SN, Crodamol DA, Speziol C18, Miglyol 812, Cosbiol type), the optional heat-insensitive lipophilic additives, if heating, and optionally the preservatives (phenoxyethanol, propylparaben type) are mixed in a beaker. The mixture is heated until homogeneity is achieved and the volatile silicone, if the latter is present in the composition, is introduced.

**Stage e:** Mixing the active phases:

The two active phases respectively obtained in a) and b) are mixed at a temperature of less than 40°C and stirring is maintained until the mixture is completely homogeneous.

**Stage f:** Introduction of the single active phase into the aqueous phase:

The single active phase obtained in stage e) is introduced into the aqueous phase obtained in stage c).

**Stage g:** (optional) Addition of the Simulgel 600PHA:

The Simulgel 600PHA is introduced with stirring into the phase obtained in f). Stirring is maintained until the Simulgel has completely dispersed.

**Stage h:** Addition of the oil or of the fatty phase obtained in d):

The single fatty phase constituent or optionally the fatty phase obtained in stage d) is introduced into the mixture obtained in f) or g).

**Stage i** (optional): Addition of the heat-sensitive additives:

The optional additives are introduced with stirring at a temperature below 40°C. Stirring is maintained until the mixture is completely homogeneous.

**Stage j** (optional): Neutralization:

The neutralization agent for the gelling agent (such as triethanolamine, the 10% sodium hydroxide solution, the citric acid/sodium citrate buffer, the succinic acid/sodium succinate buffer) or the pH buffer is introduced, if necessary, at a temperature below 40°C until at the desired pH. The product then assumes a thicker consistency. If necessary, the adjustment to 100% with water is carried out. The product is

homogenized a final time in order to ensure the active principles, adapalene and benzoyl peroxide, are satisfactorily dispersed (microscopic observation revealing a homogeneous and aggregate-free dispersion) and then the product is packaged.

**Stage k**: Correction of the water loss:

The water loss during the preparation of the product is calculated and the lost water is re-added with stirring. Stirring is maintained until the mixture is completely homogeneous.

The present invention will now be illustrated by means of the following examples.

The formulation examples below make it possible to illustrate the compositions according to the invention without, however, limiting the scope thereof. Examples of processes for the preparation of the compositions according to the invention, mentioned without implied limitation.

More specifically, by way of example, the alternative process for the preparation of the composition according to the invention comprises the following stages:

**Stage a'**: Preparation of the single active phase:

Stages a) and b) of the main process are combined, so as to obtain stage a'), which corresponds to the mixing of at least one retinoid and benzoyl peroxide with water and at least one wetting agent until they have completely dispersed, in order to obtain the single active phase.

Stages c), d), f), g), h), i), j) and k) of the main process remain unchanged. As regards stage e), this is deleted.

The present invention will now be illustrated by means of the following examples and of the following physical and chemical stability data.

The formulation examples below make it possible to illustrate the compositions according to the invention without, however, limiting the scope thereof.

The term "physical stability of the formulations"

is understood to mean carrying out macroscopic and microscopic observation at ambient temperature and 40°C, carried out at T1 month and T2 months.

Microscopic observation makes it possible to evaluate the quality of the dispersion of the two active principles. The adapalene is observed in fluorescent light while the benzoyl peroxide is observed in polarized light.

The characterization of the finished product is completed by a measurement of the yield point and of viscosity.

For the measurement of the yield point, use is made of a Haake rheometer of VT550 type with an SVDIN measuring spindle.

The rheograms are produced at 25°C and at the shear rate of 4 $s^{-1}$, 20 $s^{-1}$ and 100 $s^{-1}$ ($\gamma$), the shear stress being measured. The term "yield point" ($\tau 0$, expressed in pascals) is understood to mean the force necessary (minimum shear stress) to overcome the cohesive forces of Van der Waals type and to bring about flow. The yield point is to be equated with the value found at the shear rate of 4 $s^{-1}$.

For the viscosity measurement, use is made of Brookfield RVDVII+ or LDVDII+ viscometers. The viscosity ranges which can be measured with the two Brookfield types are as follows:

RVDVII+: 100 cP-40 McP

LVDVII+: 15 cP-6 McP

The chemical stability is ensured by an HPLC quantitative determination of the active principles.

The result is expressed in g/g of adapalene and of benzoyl peroxide and as % with respect to the expected content.

**Example 1: Formulation of cream gel type comprising 0.1% adapalene and 2.5% benzoyl peroxide**

The formulation is prepared according to the procedure described above.

| **Constituents** | **Content (% w/w)** |
|---|---|
| Benzoyl peroxide | 2.50 |
| Adapalene | 0.10 |
| Propylene glycol | 5.00 |
| Synperonic PE/L44 | 0.20 |
| EDTA | 0.10 |
| Glycerol | 5.00 |
| Xantural 180 | 0.10 |
| Carbopol Ultrez 20 | 0.70 |
| Marcol 152 | 7.00 |
| Purified water | q.s. for 100% |
| Sodium hydroxide, 10% w/w | q.s. for pH 5.5 ± 0.5 |

Stability data:

- Physical stability:

| **Characterizations at T0** | | |
|---|---|---|
| Macroscopic appearance | | White cream gel |
| Microscopic appearance | | Dispersion of the active principles without aggregates of greater than 100 $\mu$m |
| pH | | 5.144 |
| Viscosity data | Haake (4 $s^{-1}$/20 $s^{-1}$/ 100 $s^{-1}$) | 94/123/187 |
| | Brookfield RVDVII+ (S28; 5 rpm) | 65 620 cP |

| | | T+1 month | T+2 months | T+3 months |
|---|---|---|---|---|
| Macroscopic appearance | AT | Identical to T0 | Identical to T0 | Identical to T0 |
| | 40°C | Identical to T0 | Identical to T0 | Identical to T0 |
| Microscopic appearance | AT | Identical to T0 | Identical to T0 | Identical to T0 |
| | 40°C | Identical to T0 | Identical to T0 | Identical to T0 |
| pH | AT | 5.10 | 5.03 | 5.09 |
| | 40°C | 4.96 | 4.74 | 4.59 |
| Haake rheology 4 $s^{-1}$/20 $s^{-1}$/100 $s^{-1}$ | | 89/121/172 | 87/117/168 | N.R. |
| Brookfield RVDVII+ viscosity (S28; 5 rpm) | | 65 775 cP | 63 820 cP | 67 505 cP |

➢ Chemical stability:

↳ **Adapalene**

| Time→ / Stability conditions↓ | | T0 | T+1 month | T+2 months |
|---|---|---|---|---|
| AT | g/g | 0.10 | 0.10 | 0.10 |
| | % of the expected content | 100 | 100 | 100 |
| 40°C | g/g | N.A. | 0.10 | 0.11 |
| | % of the expected content | N.A. | 100 | 110 |

↳ **Benzoyl peroxide**

| Time→ / Stability conditions↓ | | T0 | T+1 month | T+2 months |
|---|---|---|---|---|
| AT | g/g | 2.7 | 2.7 | 2.7 |
| | % of the expected content | 108 | 108 | 108 |
| 40°C | g/g | N.A. | 2.6 | 2.6 |
| | % of the expected content | N.A. | 104 | 104 |

**Example 2: Formulation of thick cream gel type comprising 0.1% adapalene and 2.5% benzoyl peroxide**

The formulation is prepared according to the procedure described above.

| **Constituents** | **Content (% w/w)** |
|---|---|
| Benzoyl peroxide | 2.50 |
| Adapalene | 0.10 |
| Propylene glycol | 6.00 |
| Synperonic PE/L44 | 0.20 |
| Glycerol | 5.00 |
| ST-Cyclomethicone 5NF | 7.00 |
| Simulgel 600 PHA | 4.00 |
| Purified water | q.s. for 100% |

➢ Physical stability:

| **Characterizations at T0** | | |
|---|---|---|
| Macroscopic appearance | | White cream gel |
| Microscopic appearance | | Dispersion of the active principles without aggregates of greater than 100 $\mu$m |
| pH | | 3.542 |
| Viscosity data | Haake (4 $s^{-1}$/20 $s^{-1}$ / 100 $s^{-1}$) | 236/296/449 |
| | Brookfield RVDVII+ (S29; 5 rpm) | 164 650 cP |

| | | T+1 month | T+2 months | T+3 months |
|---|---|---|---|---|
| Macroscopic appearance | AT | Identical to T0 | Identical to T0 | Identical to T0 |
| | 40°C | Identical to T0 | Identical to T0 | Identical to T0 |
| Microscopic appearance | AT | Identical to T0 | Identical to T0 | Identical to T0 |
| | 40°C | Identical to T0 | Identical to T0 | Identical to T0 |
| pH | AT | 3.47 | 3.36 | 3.50 |
| | 40°C | 3.31 | 3.17 | 3.27 |
| Haake rheology 4 $s^{-1}$/20 $s^{-1}$/100 $s^{-1}$ | | 223/286/389 | 201/268/334 | N.R. |
| Brookfield RVDVII+ viscosity (S29; 5 rpm) | | 159 070 cP | 150 160 cP | 132 720 cP |

➢ Chemical stability:

↳ **Adapalene**

| Time→ / Stability conditions↓ | | T0 | T+1 month | T+2 months |
|---|---|---|---|---|
| AT | g/g | 0.10 | 0.11 | 0.10 |
| | % of the expected content | 100 | 110 | 100 |
| 40°C | g/g | N.A. | 0.10 | 0.10 |
| | % of the expected content | N.A. | 100 | 100 |

↳ **Benzoyl peroxide**

| Time→ / Stability conditions↓ | | T0 | T+1 month | T+2 months |
|---|---|---|---|---|
| AT | g/g | 2.7 | 2.8 | 2.7 |
| | % of the expected content | 108 | 112 | 108 |
| 40°C | g/g | N.A. | 2.6 | 2.6 |
| | % of the expected content | N.A. | 104 | 104 |

**Example 3: Formulation of fluid cream gel type comprising 0.3% adapalene and 1% benzoyl peroxide**

The formulation is prepared according to the procedure described above.

| **Constituents** | **Content (% w/w)** |
|---|---|
| Benzoyl peroxide | 1.00 |
| Adapalene | 0.30 |
| Lauroglycol | 2.00 |
| Synperonic PE/L62 | 0.20 |
| EDTA | 0.10 |
| Methylparaben | 0.20 |
| Methocel E4M Premium | 0.10 |
| Carbopol ETD202NF | 0.30 |
| Olepal isostearique | 2.00 |
| Cosbiol | 8.00 |
| Cetiol SN PH | 8.00 |
| Propylparaben | 0.05 |
| Sodium hydroxide, 10% w/w | q.s. for pH 5.5 ± 0.5 |
| Purified water | q.s. for 100% |

**Example 4: Formulation of fluid cream gel type comprising 0.10% adapalene and 0.25% benzoyl peroxide**

The formulation is prepared according to the procedure described above.

2007344298 07 Jun 2013

| Constituents | Content (% w/w) |
|---|---|
| Benzoyl peroxide | 0.25 |
| Adapalene | 0.10 |
| Propylene glycol | 2.00 |
| Synperonic PE/L62 | 0.20 |
| EDTA | 0.10 |
| Glycerol | 5.00 |
| Methylparaben | 0.20 |
| Carbopol Ultrez-20 | 0.30 |
| Veegum K | 0.20 |
| Xanthan gum | 0.20 |
| ST-Cyclomethicone 5NF | 7.00 |
| Propylparaben | 0.10 |
| Triethanolamine | q.s. for pH 5.5 ± 0.5 |
| Purified water | q.s. for 100% |

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

2007344298 07 Jun 2013

## CLAIMS

1. Composition in the form of a cream gel comprising, in a physiologically acceptable medium, dispersed adapalene and dispersed benzoyl peroxide, and at least one lipophilic compound making up a fatty phase, and wherein the composition is devoid of any emulsifying agent.

2. Composition according to Claim 1, wherein the composition comprises between 0.0001 and 20% of adapalene.

3. Composition according to Claim 1 or Claim 2, wherein the composition comprises between 0.0001 and 20% of benzoyl peroxide.

4. Composition according to any one of the preceding claims, wherein the benzoyl peroxide is in an encapsulated or free form.

5. Composition according to any one of the preceding claims, wherein the composition is physically and chemically stable.

6. Composition according to any one of claims 1 to 5, wherein the lipophilic compound is chosen from vegetable, mineral, animal or synthetic oils, silicone oils and their mixtures.

7. Composition according to Claim 7, wherein the lipophilic compound is chosen from liquid paraffins, sweet almond oil, palm oil, soybean oil, sesame oil, sunflower oil, lanolin, squalene, fish oil, mink oil, squalane, cetearyl isononanoate, isopropyl palmitate, diisopropyl adipate, caprylic/capric triglyceride, a volatile or nonvolatile silicone oil and natural or

2007344298 07 Jun 2013

synthetic waxes.

8. Composition according to any one of the preceding claims, wherein the composition comprises at least one pH-independent gelling agent.

9. Composition according to Claim 8, wherein the composition comprises between 0.001 and 15% of gelling agent.

10. Composition according to Claim 8 or Claim 9, wherein the gelling agent is chosen from compounds of the family of polyacrylamides; "electrolyte-insensitive" carbomers; polysaccharides; cellulose and its derivatives; and magnesium aluminium silicates.

11. Composition according to Claim 10, wherein the gelling agent is chosen from sodium acryloyldimethyltaurate copolymer/isohexadecane/polysorbate 80 mixture, the polyacrylamide/C13-14 isoparaffin/laureth-7 mixture, Acrylates/ C10-30 Alkyl Acrylate Crosspolymer, xanthan gum, hydroxypropylmethylcellulose and hydroxyethylcellulose.

12. Composition according to any one of the preceding claims, wherein the composition comprises a wetting agent.

13. Composition according to Claim 12, wherein the composition comprises between 0.001 and 20% of wetting agent.

14. Composition according to Claim 12 or Claim 13, wherein the wetting agent is chosen from a poloxamer and propylene glycol.

2007344298 07 Jun 2013

15. Composition according to any one of the preceding claims, wherein the composition comprises the ingredients (expressed as percentage by weight) chosen from:

- from 0.001% to 5%, of adapalene;
- from 0.025% to 10%, of benzoyl peroxide;
- from 30% to 95%, of water;
- from 0.01% to 15%, of one or more gelling agents and/or suspending agents and/or pH-independent gelling agents;
- from 2% to 50%, of fatty phase;
- from 0% to 1.5%, of chelating agents;
- from 0% to 10%, of one or more wetting agents;
- from 0% to 3%, of preservatives;
- from 0% to 20%, of humectants and/or emollients;
- from 0% to 3%, of stabilizing agents;
- from 0% to 10%, of neutralizing agents.

16. Composition according to any one of the preceding claims, wherein the composition comprises the ingredients (expressed as percentage by weight) chosen from:

- from 0.01% to 0.5%, of adapalene;
- from 2% to 10%, of benzoyl peroxide;
- from 50% to 85%, of water;
- from 0.1% to 5%, of one or more gelling agents and/or suspending agents and/or pH-independent gelling agents;
- from 5% to 30%, of fatty phase;
- from 0.05% to 0.5%, of chelating agents;
- from 2% to 7%, of one or more wetting agents;
- from 0.05% to 1%, of preservatives;
- from 2% to 15%, of humectants and/or emollients;
- from 0.05% to 2%, of stabilizing agents;
- from 0.1% to 5%, of neutralizing agents.

17. Composition according to any one of Claims 1 to 16, as a medicament.

2007344298 07 Jun 2013

18. Process for the preparation of the composition according to any one of Claims 1 to 16, wherein the process successively comprises the following stages:

a) mixing adapalene with water until it is completely dispersed, in order to obtain active phase 1;

b) mixing benzoyl peroxide with water until it has completely dispersed, in order to obtain active phase 2;

c) mixing at least one gelling agent and/or suspending agent and/or pH-independent gelling agent with water, optionally one or more chelating agents, one or more preservatives, one or more humectants and/or emollients, one or more stabilizing agents and the hydrophilic additives, in order to obtain the aqueous phase;

d) optionally, mixing at least two lipophilic compounds, in order to obtain the fatty phase;

e) mixing the 2 active phases obtained in a) and b), in order to obtain a single active phase;

f) introducing the single active phase obtained in e) into the aqueous phase obtained in c);

g) introducing the single compound of the fatty phase or optionally the fatty phase obtained in d), in order to obtain a cream gel;

h) optionally adding, the heat-sensitive additives;

i) optionally adding, a neutralizing agent for the gelling agent into the cream gel obtained in g) or h);

j) optionally, further adding water.

19. Process for the preparation of the composition according to Claim 18, wherein the process successively comprises the following stages:

a) adapalene is mixed with at least one wetting agent in water until the adapalene has completely dispersed, in order to obtain active phase 1;

b) the benzoyl peroxide is mixed with at least one wetting agent in water until it has completely

2007344298 07 Jun 2013

dispersed, in order to obtain active phase 2;

c) one or more gelling agents and/or suspending agents and/or pH-independent gelling agents (with the exception of the polyacrylamide) and optionally one or more chelating agents, one or more preservatives, one or more humectants and/or emollients, one or more stabilizing agents and the heat-insensitive hydrophilic additives are dissolved in the water with stirring, if necessary under hot conditions. Stirring is maintained and optional heating is maintained until homogeneity is achieved, in order to obtain the aqueous phase;

d) optionally adding, at least oils, and optionally solid fatty substances, and preservatives and the heat-insensitive lipophilic additives are mixed, optionally under hot conditions, until homogeneity is achieved, in order to obtain the fatty phase;

e) active phases 1 and 2 are mixed, so as to obtain a single active phase;

f) the single active phase obtained in e) is added to the aqueous phase obtained in c);

g) optionally introducing, the polyacrylamide into the phase obtained in f);

h) the single fatty phase constituent or optionally the said fatty phase obtained in d) is introduced into the phase obtained in f) or g), in order to obtain a cream gel;

i) optionally adding, the heat-sensitive additives;

j) optionally adding, a neutralizing agent for the gelling agent into the cream gel obtained in h) or i), in order to obtain the desired pH;

k) optionally, further adding water.

20. Use of a composition according to any one of Claims 1 to 16 for preventing or treating dermatological conditions linked to disorders of cell differentiation and/or proliferation and/or of keratinisation.

2007344298 07 Jun 2013

21. Use of a composition according to any one of Claims 1 to 16 in the manufacture of a pharmaceutical preparation for preventing or treating acne vulgaris.

22. Use of a composition according to Claim 20 or Claim 21 in the manufacture of a pharmaceutical preparation.

23. Cosmetic use of a composition according to any one of Claims 1 to 16 for the treatment of skin with a tendency towards acne, for causing hair growth or preventing hair loss, for combating the greasy appearance of the skin or hair, in protecting against the harmful effects of the sun or for preventing and/or combating photoinduced or chronologic ageing.

24. A method of treatment or prevention of dermatological condition, linked to disorders of cell differentiation and/or proliferation and/or keratinisation, or of acne vulgaris, by administering to a subject in need of treatment or prevention thereof a composition according to any one of Claims 1 to 16.

25. A composition according to claim 1, a process for the preparation of the composition; or use or methods of treatment involving the composition, substantially as herein described with reference to the accompanying Examples thereof.