

and then mixed with entire quantity of cream. Diethanolamine was further mixed in and the cream was passed through triple roller mill prior to filling in the tubes.

Example 7

- 5 This example illustrates the present invention in the form of a cream of a combination of RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H benzo [i,j] quinolizine-2-carboxylic acid, clobetasol propionate and miconazole nitrate. The pharmaceutical composition of this example is given below in table 7.

10

Table 7

Ingredients	% Weight of the composition
Active antibacterial	1.00
Miconazole Nitrate	2.00
Clobetasol Propionate	0.05
Disodium edetate	0.10
Propylene glycol	10.00
Methyl paraben	0.18
Propyl paraben	0.02
Cetostearyl alcohol	7.20
Liquid paraffin (heavy)	15.00
Microcrystalline wax	3.00
Cetomacrogol – 1000	2.00
Dimethicone	0.10
α-Tocopherol	0.03
Diethanolamine	0.30
Purified water	q.s. to 100.00

Cetostearyl alcohol, liquid paraffin, microcrystalline wax, cetomacrogol and dimethicone were mixed and heated to 70°C. An aqueous solution 43% (w/v) of disodium edetate was also heated to 70°C and added to the above mixture under homogenization to form an emulsion. Dispersion
5 of methyl paraben and propyl paraben in a part of propylene glycol was added to the emulsion, which was cooled to room temperature to form a cream. α -tocopherol was further dispersed in this cream. Clobetasol propionate dissolved in the remaining portion of propylene glycol, active antibacterial ingredient and miconazole nitrate were triturated with part quantity of cream and then mixed with entire quantity of cream. Diethanolamine was further mixed in, and the cream
10 was passed through triple roller mill prior to filling in the tubes.

Example 8

15 This example illustrates the present invention in the form of a cream of a combination of RS-($\pm$)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H benzo[i,j] quinolizine-2-carboxylic acid and miconazole nitrate. The pharmaceutical composition of this example is given below in table 8.

Table 8

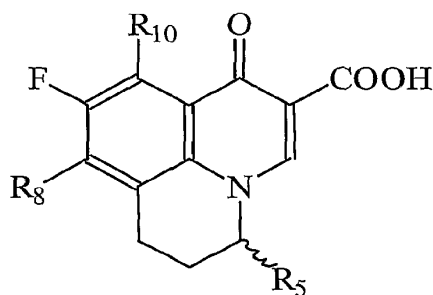
Ingredients	% Weight of the composition
Active antibacterial	1.00
Miconazole Nitrate	2.00
Disodium edetate	0.10
Propylene glycol	10.00
Methyl paraben	0.18
Propyl paraben	0.02
Cetostearyl alcohol	7.20
Liquid paraffin (heavy)	15.00
Microcrystalline wax	3.00
Cetomacrogol – 1000	2.00
Dimethicone	0.10
α -Tocopherol	0.03
Diethanolamine	0.30
Purified water	q.s. to 100.00

Cetostearyl alcohol, liquid paraffin, microcrystalline wax, cetomacrogol and dimethicone were mixed and heated to 70°C. An aqueous solution 40 % (w/v) of disodium edetate was also heated to 70°C and added to the above mixture under homogenization to form an emulsion. Dissolved methyl paraben and propyl paraben in propylene glycol and added to the emulsion, which was cooled to room temperature to form a cream. α -tocopherol was further dispersed in this cream. Active antibacterial ingredient and miconazole nitrate were triturated with part quantity of cream and then mixed with entire quantity of cream. Diethanolamine was further mixed in, and the cream was passed through triple roller mill prior to filling in the tubes.

CLAIMS

1. A stable pharmaceutical composition comprising:

a pharmaceutically effective amount of benzoquinolizine-2-carboxylic acid antimicrobial
5 drug of the formula:



(I)

wherein:

15 R_5 is C_{1-6} alkyl, as a mixture of enantiomers or in a stereochemical orientation;

R_8 is 4-hydroxypiperidinyl optionally further substituted with one or more C_{1-6} alkyl,
hydroxypiperidinyl optionally further mono/poly substituted with C_{1-6} alkyl;

R_{10} is selected from H, C_{1-5} alkyl, amino, alkylamino and acylamino groups;

or an optical isomer, diastereomer or enantiomer thereof, or polymorphs and

20 pseudopolymorphs or prodrugs thereof or pharmaceutically acceptable salts and

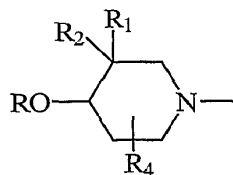
hydrates thereof or mixtures thereof; singly or in combination with

a pharmaceutically effective amount(s) of a retinoid, an antibacterial, a steroid/non-
steroid antiinflammatory agent, an antifungal agent or mixtures thereof.

25 2. The composition of claim 1 wherein in the formula (I),

R_5 is CH_3 , in S-orientation.

R_8 is



(II)

wherein:

R is hydrogen, C₁-C₆ alkyl, glycosyl, aralkyl, C₁-C₆ alkanoyl, or aminoalkanoyl or R is C₆H₁₁O₆, PO₃H₂ or SO₃H thus giving respectively the gluconic acid, phosphoric acid and sulfonic acid ester derivatives of the compounds;

5 R₁ and R₂ are the same or different and represent H, C₁₋₄ alkyl, aralkyl, aminoalkyl, trifluoroalkyl or halogen;

R₄ is H, C₁₋₄ alkyl, CF₃, phenyl, or F; R₄ is present at one or more of the positions of 2-, 4-, 5-, or 6- of the piperidine ring; and

R₁₀ is selected from H, C₁₋₅ alkyl, amino, alkylamino or acylamino groups.

- 10 3. The composition of claim 1 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is selected from the group consisting of

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

15 R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

20 RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

25 S(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

30 R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

S(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

S(-)-9-fluoro-6,7-dihydro-8-{trans-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-{cis-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl}-5-methyl-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-{cis-(-)-4-R-hydroxy-3-S-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid;

5 S-(-)-9-fluoro-6,7-dihydro-8-{cis-(+)-4-S-hydroxy-3-R-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid; and

S-(-)-9-fluoro-6,7-dihydro-8-(3-ethyl-4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid (mixture of cis racemate and trans racemate) and pure stereoisomers thereof.

10

4. The composition of claim 3 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof.

15

5. The composition of claim 3 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid 0.2 hydrate.

20

6. The composition of claim 3 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid.

25

7. The composition of claim 1 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug comprises about 0.1 – 10 % by weight of the composition.

8. The composition of claim 1 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug comprises about 1 % by weight of the composition.

30

9. The method of claim 1 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug comprises about 0.5 % by weight of the composition.

10. The composition of claim 1 wherein said retinoid is selected from the group consisting essentially of benzoyl peroxide, dichloroacetic acid, glutaraldehyde, resorcinol, retinoic acid,

salicylic acid, adapalene, algestone acetophenide, azelaic acid, benzoyl peroxide, cioteronel, ciproterone, isotretinoin, motretinide, tretinoin, tazarotene, tioxolone, combinations and mixtures thereof.

5 11. The composition of claim 9 wherein the retinoid comprises adapalene.

12. The composition of claim 1 wherein said antibacterial is selected from the classes of aminoglycosides, cephalosporins, diaminopyridines, oxazolidinones, sulfonamides, tetracyclines or combinations of these classes.

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13. The composition of claim 1 wherein said steroid is selected from the group consisting essentially of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chlorprednisone, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, 15 desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucoronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, 20 meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 21-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, pimexolone, tixocortol, triamcinolone, triamcinoloneacetonide, triamcinolone benetonide, triamcinolone hexacetonide, 25 combinations and mixtures thereof.

14. The composition of claim 13 wherein the steroid comprises clobetasol.

15. The composition of claim 13 wherein the steroid comprises mometasone.

30

16. The composition of claim 1 wherein said non-steroid antiinflammatory agent is selected from the group consisting essentially of ibuprofen, indomethacin, ketoprofen, flurbiprofen, celecoxib, valdecoxib, rofecoxib, varecoxib, parecoxib, meloxicam, nimesulide, etodolac, combinations and mixtures thereof.

17. The composition of claim 1 wherein said antifungal agent is selected from the classes of polyenes, allylamines, imidazoles, thiocarbamates, triazoles or combinations of these classes.
18. The composition of claim 1 wherein said antifungal agent is selected from amphotericin, nystatin, caspofungin, griseofulvin, oligomycins, butenafine, naftifine, terbinafine, bifonazole, clotrimazole, ketoconazole, miconazole, liranafate, tolnaftate, fluconazole, itraconazole, or voriconazole.
19. The composition of claim 18 wherein the antifungal agent comprises butenafine.
20. The composition of claim 1 wherein the pharmaceutically acceptable vehicle further comprises a pH modifying agent selected from acids, bases, inorganic basic salts, organic basic salts, buffering agents or mixtures thereof.
21. The composition of claim 1 that is in a physical form selected from drops, pastes, ointments, creams, milks, pomades, powders, impregnated pads, tules, solutions, gels, shampoos, lotions, suspensions, microspheres, nanospheres, lipidic vesicles, polymeric vesicles, polymeric patches or biological inserts.
22. A method of treating and/or preventing a bacterial infection disease comprising: administering to a subject in need thereof, a pharmaceutical composition comprising: a pharmaceutically effective amount of benzoquinolizine-2-carboxylic acid antimicrobial drug of the formula (I) according to claim 1; singly or in combination with a pharmaceutically effective amount(s) of a retinoid, an antibacterial, a steroid/non-steroid antiinflammatory agent, an antifungal agent or mixtures thereof.
23. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof.
24. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-

benzo[i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof.

25. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug
5 is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-
benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate.
26. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug
is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-
10 benzo[i,j]quinolizine-2-carboxylic acid.
27. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug
comprises about 0.1 – 10 % by weight of the composition.
- 15 28. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug
comprises about 1 % by weight of the composition.
29. The method of claim 22 wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug
comprises about 0.5 % by weight of the composition.
- 20 30. The method of claim 22 wherein the retinoid comprises adapalene.
31. The method of claim 22 wherein said antibacterial is selected from the classes of
aminoglycosides, cephalosporins, diaminopyridines, oxazolidinones, sulfonamides,
25 tetracyclines or combinations of these classes.
32. The method of claim 22 wherein the steroid comprises clobetasol.
33. The method of claim 22 wherein said non-steroid antiinflammatory agent is selected from the
30 group consisting essentially of ibuprofen, indomethacin, ketoprofen, flurbiprofen, celecoxib,
valdecoxib, rofecoxib, varecoxib, parecoxib, meloxicam, nimesulide, etodolac, combinations
and mixtures thereof.
34. The method of claim 22 wherein the antifungal agent comprises butenafine.

35. The method of claim 22 wherein said composition is in a physical form selected from concentrates, drops, pastes, ointments, creams, milks, pomades, powders, impregnated pads, tulle, solutions, gels, sprays, shampoos, lotions, suspensions, microspheres, nanospheres, lipidic vesicles, polymeric vesicles, polymeric patches or biological inserts.

5

36. The method of claim 22 wherein the subject is an animal or human.

37. The method of claim 22 wherein the route of administration is selected from ocular, nasal, otic, rectal, vaginal, intradermal, intratumoral, intralesional, intravascular, topical, transdermal, local, regional, or loco-regional.

10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 03/00422

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/473 A61P31/04

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 A61P

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, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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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

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Z document member of the same patent family

Date of the actual completion of the international search

3 June 2004

Date of mailing of the international search report

16/06/2004

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INTERNATIONAL SEARCH REPORT

national Application No
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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IN 03/00422

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (patent family annex) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

RU/IN 03/00422

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(54) Title: DELIVERY OF HYDROPHOBIC BIOACTIVE AGENTS

(57) Abstract: A composition for delivery of a hydrophobic bioactive agent is provided that provides for a partially solubilized storage solution that upon exposure to the air results in a fully solubilized bioactive agent in a molecular form for optimal delivery to the skin of a subject. The composition is used for the therapeutic treatment or diagnosis of numerous skin conditions such as acne, wrinkles, inflammation, and epidermal or musculoskeletal pain.

DELIVERY OF HYDROPHOBIC BIOACTIVE AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application depends from and claims priority to U.S. Provisional Application No. 61/393,615 filed October 15, 2010, and PCT/US2010/025491 filed February 26, 2010 which
5 claims priority to U.S. Provisional Application No. 61/286,668 filed December 15, 2009.

FIELD OF THE INVENTION

[0002] This invention relates to compositions and methods for delivery of water insoluble or hydrophobic bioactive agents to the skin.

BACKGROUND OF THE INVENTION

10 **[0003]** Lipophilic skin care active agents such as retinoids are generally applied topically to reduce the appearance of aging, for other cosmetic purposes, or to treat a skin condition such as acne.

[0004] The comfort associated with application of topical agents is related in part to the rate of evaporation of the applied composition on the skin. A product with a slow evaporation rate
15 could feel greasy on the skin whereas a product with an overly rapid evaporation rate feels either as if it has not been applied to the skin at all or leaves the user with the impression that not enough has been applied possibly leading to overuse. Combining topical agents with volatile silicones allows the proper evaporation rate to provide a pleasing application. Silicones, however, by themselves are poor solvents for hydrophobic organic active agents.

20 **[0005]** To address the poor solubility in silicones, delivery systems for these agents commonly require 35% or more organic solvent as a carrier to solubilize the active agent as well as provide suitability for combination with volatile compounds that provide pleasing application by the user. The prior art prefers alcohols such as ethyl alcohol as an organic solvent.

[0006] Many active agents contribute to thinning or drying of the skin. This problem is
25 worsened by including significant levels of organic solvents that themselves can alter epidermal barrier lipids and contribute to skin irritation. Ethyl alcohol as used in the retinoid composition of U.S. Patent No. 4,826,828 was believed to be the solution for topical delivery of hydrophobic agents. Ethyl alcohol, to the contrary, contributes to skin irritation and dryness. Thus, combining ethyl alcohol with potentially irritating active agents increases skin dryness leading to
30 non-optimal use.

[0007] Thus, there exists a need for a hydrophobic active agent delivery system that provides pleasing application and does not contribute to toxicity.

SUMMARY OF THE INVENTION

- 5 [0008] The following summary of the invention is provided to facilitate an understanding of some of the innovative features unique to the present invention and is not intended to be a full description. A full appreciation of the various aspects of the invention can be gained by taking the entire specification, claims, drawings, and abstract as a whole.
- 10 [0009] A composition suitable for delivery of a bioactive agent to the skin of a subject is provided. A composition includes a bioactive agent, a non-volatile solvent into which the bioactive agent is soluble, a carrier, and a thickener. A bioactive agent in some embodiments is a vitamin A derivative, corticosteroid, hydroxy acid, antimicrobial, anti-inflammatory, or a combination thereof. A carrier is a compound that has sufficient volatility to vaporize upon application of the composition to the skin of a subject, and optionally at standard temperature
- 15 and pressure.
- [0010] A bioactive agent is appreciated to be present in the composition at a first concentration where the concentration of the bioactive agent increases upon volatilization of the carrier. The bioactive agent is optionally in molecular (solubilized) form, microcrystalline form, or partly in both forms. As such, a bioactive agent is optionally less than 100% in solution. In
- 20 some embodiments, a bioactive agent is a retinoid such as hydroxyanastil retinoate, or a corticosteroid such as halobetasol. Halobetasol is optionally present at 0.025 to 0.05 percent by weight.
- [0011] A solvent is optionally dimethylisobutide, ethoxydiglycol, or a combination thereof.
- [0012] Some embodiments include an opacifier, illustratively titanium dioxide.
- 25 [0013] Processes for forming a composition are also provided that include dissolving a bioactive agent in a non-volatile solvent, and combining a carrier with the solvent such that the presence of said carrier places at least a portion of said bioactive agent in a crystalline state. A thickener optionally is added to the carrier prior to or following combining the carrier with the bioactive agent and non-volatile solvent.
- 30 [0014] Processes of treating one or more skin conditions are also provided. The processes include administering an inventive composition to a subject with a skin condition. The composition is optionally administered topically. Frequency of administration is optionally from

one to three times daily. A skin condition is optionally acne, wrinkles, musculoskeletal pain, inflammation, dryness, eczema, psoriasis, actinic keratoses, nonactinic keratoses, or rosaceous.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0015] The following description of particular embodiment(s) is merely exemplary in nature and is in no way intended to limit the scope of the invention, its application, or uses, which may, of course, vary. The invention is described with relation to the non-limiting definitions and terminology included herein. These definitions and terminology are not designed to function as a limitation on the scope or practice of the invention but are presented for illustrative and descriptive purposes only. While the processes or compositions herein are described as an order of individual steps or using specific materials, it is appreciated that described steps or materials may be interchangeable such that the description of the invention includes multiple parts or steps arranged in many ways as is readily appreciated by one of skill in the art.

[0016] The invention has utility for efficient delivery of one or more hydrophobic bioactive agents to a subject. A composition is provided whereby a bioactive agent is not completely solubilized until application to the skin of a subject whereby upon evaporation of a volatile solvent the bioactive agent becomes fully solubilized to a molecular form. A composition includes:

- A volatile carrier in which a bioactive agent is essentially insoluble;
- A non-volatile solvent in which the bioactive agent is soluble; and
- A thickener.

[0017] The bioactive agent is first dissolved in the non-volatile solvent, then that solution is added to the volatile carrier to create a system where the bioactive agent is partly in solution and partly in a microcrystalline state. The microcrystals are distributed uniformly within the gel created by the thickener. When this composition is applied to the skin surface, the volatile portion evaporates leaving essentially the bioactive agent, non-volatile solvent and thickener. The bioactive agent goes into solution and reaches optimal biological activity in molecular form. The non-volatile solvent can be used at a concentration such that the solution forming on the skin surface is optimally in a saturated or super-saturated state, enhancing percutaneous penetration in the skin.

[0018] One or more of several bioactive agents are used with the compositions. When the term bioactive agent is used herein, it is appreciated to be equally applicable to the singular one

bioactive agent as well as to a plurality of bioactive agents. Some embodiments include a single bioactive agent only. Some embodiments include a plurality of bioactive agents.

[0019] As used herein the term “bioactive agent” refers to a molecule suitable for delivery to the skin or mucosal regions of a subject. Optionally, an active agent has pharmaceutical activity and is present for the treatment or prevention of a skin condition. Active agents are optionally low polarity molecules such as those having a hydrocarbon chain of three or more carbons, but may also comprise materials of higher polarity. Illustrative examples include retinol (vitamin A), retinal, retinyl ester, retinol, tretinoin (all-trans-retinoic acid), isotretinoin, adapalene, tazarotene, and 13-cis-retinoic acid, as well as a variety of esters and similar derivatives. A bioactive agent is optionally one or more esters and amides of 9-cis-retinoic acid such as those described in U.S. Patent No: 5,837,728. A bioactive agent is optionally one or more of esters or amides of trans-retinoic acid such as those found in U.S. Pat. No. 4,055,659 (all-trans-retinoyloxyacetamide), U.S. Pat. No. 4,126,697 (4-(all-trans-retinoyloxyacetyl)-catechol), U.S. Pat. No. 4,126,698 (2-hydroxyethyl all-trans-retinoate), and U.S. Pat. No. 4,304,787 (benzyl all-trans-retinoate), as well as mixtures of these and other bioactive agents. A bioactive agent is optionally a retinoid such as those described in U.S. Patent Application Publication No: 2008/0139518.

[0020] A bioactive agent is not limited to vitamin A and its derivatives. One or more other bioactive agents are similarly suitable for inclusion in a composition as a bioactive agent. Illustrative examples include hydroxy acids; aromatic molecules such as benzoyl peroxide and resorcinol; antimicrobials such as azelaic acid, erythromycin, sodium sulfacetamide, tetracycline and derivatives, and clindamycin; anti-neoplastic agents and/or ophthalmic agents illustratively including 5-fluorouracil, doxorubicin, imiquimod, and sodium [*o*-(2,6-dichloranilino) phenyl] acetate; anti-viral agents illustratively ganciclovir, trifluorothymidine and related compounds; steroidal anti-inflammatory agents; nonsteroidal anti-inflammatory agents illustratively flurbiprofen, ibuprofen, naproxen, indomethacin and related compounds; anti-mitotic drugs illustratively colchicine taxol and related compounds; drugs that act on actin polymerization illustratively phalloidin, cytochlasin B and related compounds; inhibitors of dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP) and/or uridine phosphorylase (UP) enzyme inhibitors; ultraviolet light (UV) filters illustratively benzophenone derivatives such as oxybenzone, octocrylene, octyl methoxycinnamate, and avobenzone; radiation proactive agents illustratively methyluracils such as 6-methyluracil and 4-methyluracil; and immunomodulating molecules such as tacrolimus, and pimecrolimus; peptides (i.e. non-enzymatic protein); enzymes;

amino acids, illustratively glutamate, glycine, alanine, valine, leucine, isoleucine, serine, threonine, arginine, lysine, aspartic acid, methionine, phenylalanine, tyrosine, proline, oxyproline, histidine, among other amino acids, both essential and non-essential known in the art, and derivatives thereof; growth factors, illustratively, epidermal growth factor, TGF- α , TGF- β , VEGF, among others known in the art; topical anesthetics, illustratively, benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine; and combinations thereof. A bioactive agent need not have pharmaceutical activity. Other bioactive agents are illustratively cosmetics such as pigments, dyes, and fillers.

5 [0021] A bioactive agent is optionally a hydroxy acid. Examples of hydroxy acids illustratively include beta hydroxyl acids such as salicylic acid, acetylsalicylic acid, and the like.

[0022] In some embodiments, a bioactive agent is a steroid or steroid derivative. Illustrative examples of steroids or steroid derivatives include the corticosteroids or corticosteroid derivatives. Examples of corticosteroids illustratively include hydrocortisone, hydrocortisone acetate, cortisone acetate, triamcinolone pivalate, prednisolone, methylprednisolone, prednisone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, flucortolone, hydrocortisone-17-valerate, acetonide, betamethasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, flucortolone caproate, flucortolone pivalate, fluprednidene acetate, hydrocortisone-17-butyrate, 17-aceponate, 17-buteprate, prednicarbate, flunisolide, fluticasone propionate, halobetasol, among others, and combinations thereof.

15 [0023] A bioactive agent is optionally a lipid such as those suitable for controlling perspiration. Lipids optionally have an HLB of less than 12, less than 8, or optionally less than 6. Illustrative examples of lipids include glyceryl monostearate, glyceryl monoisostearate, glyceryl monomyristate, glyceryl monooleate, diglyceryl monoisostearate, propylene glycol monostearate, propylene glycol monoisostearate, propylene glycol monocaprylate, sorbitan monoisostearate, sorbitan monocaprylate, sorbitan monoisoleate, glyceryl monolaurate, glyceryl monocaprylate, glyceryl monocaprate, mixtures thereof or the like. Optionally, the lipid is glyceryl monolaurate, made available by suppliers like Fitz Chem Corporation under the name MONOMULS 90-L12.

25 [0024] A lipid optionally makes up from about 4 to about 35%, and optionally, from about 5 to about 20%, and optionally, from about 10 to about 15% by weight of the composition, based on total weight of the composition and including all values and ranges between 4% to 35%.

[0025] The compositions of the invention optionally include 0.005 to 1.0 weight percent retinol, in which case they are optionally applied directly to the skin, or supplied as more concentrated solution containing higher levels of active agent, in which case prior to application they are diluted optionally by means of a cosmetically acceptable carrier to a desired level such as 0.005 to 2.0 weight percent for retinol.

[0026] It is appreciated that an inventive composition optionally includes more than one bioactive agent. Optionally, 2, 3, 4, 5, 6, or more bioactive agents are present in an inventive composition. An active agent is optionally a prodrug that is converted to a desired active species optionally in the skin or layer thereof.

[0027] Optionally, a bioactive agent is present in less than 30 percent w/w amounts. Optionally, active agent is present at a weight percent of 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5, 0.1, 0.01, 0.001, 0.0001, any level in between or any range between 30% and 0.0001 percent by weight. Optionally, a bioactive agent is present at 20 percent w/w. Illustratively, when azelaic acid is an active agent it is present at 15 to 25 percent w/w. A vitamin A derivative is optionally present at 0.001 to 2 percent by weight. Imiquimod is optionally present at 3 to 8 percent by weight. Benzoyl peroxide is optionally present at 1 to 10 percent by weight. A steroid or steroid derivative is optionally included in a composition at 0.01 to 10% or more by weight. Optionally, a steroid is present at from 0.01 to 1% by weight, optionally 0.02 to 0.08% by weight, optionally 0.025 to 0.05% by weight. As examples of some embodiments, halobetasol is present at 0.025 to 0.05% by weight.

[0028] In some formulations of the invention, water is optionally minimized or eliminated to improve the stability of retinol and to minimize the potential for separation of the oil and water. Optionally, water is present at less than 2%. One of ordinary skill in the art will recognize that differing levels of active agent will be operable herein depending on the desired final amount of active agent at administration.

[0029] A bioactive agent delivery composition includes a carrier that is a volatile solvent. A volatile carrier that has a boiling point and heat of vaporization such that it will volatilize at one atmosphere at the temperature of the surface of the skin of a subject, illustratively, at or in excess of 32°C. A bioactive agent is optionally insoluble in a carrier. A bioactive agent is optionally soluble in a carrier at the level present in the composition such that when the bioactive agent and solvent are combined with the carrier, the entire portion of the bioactive agent remains in molecular form. A volatile carrier includes volatile compounds such as volatile silicones.

- Silicones are illustratively cyclic silicones or non-cyclic silicones. Examples of cyclic silicones illustratively include cyclic polydiorganosiloxanes, cyclotetradimethicones and cyclopentadimethicones. Linear organopolysiloxanes are illustratively alkyl-, alkoxy- or phenyldimethicones, and alkyl-, alkoxy- or phenyltrimethicones. Optionally, a carrier is an aliphatic volatile silicone. Aliphatic volatile silicones optionally have from two to six silicon atoms. Optionally, an aliphatic volatile silicone is a linear polyorganosiloxane such as a polyorganosiloxane with 2 to 6 silicon atoms, optionally, trisiloxane. Optionally, a carrier is ethyl trisiloxane. It is appreciated that an inventive composition optionally includes more than one carrier.
- 10 [0030] Volatile silicones optionally are lightweight carriers that evaporate on application and thus have an elegant, light-weight “feel” on the skin. Volatile silicones are typically limited in their ability to dissolve low polarity (i.e. usually greater than C7-C8)) organic compounds, illustratively, retinoids. For example, when relatively low therapeutic levels of retinol (0.1-0.2% w/v) are dissolved in cyclomethicone alone, hazy solutions result due to incomplete solubilization by the silicone fluid.
- 15 [0031] Some embodiments include a vehicle. A vehicle is optionally an organic polyhalogenic vehicle. Organic polyhalogenic vehicles are optionally those disclosed in US Patent No: 6,251,375. In particular instances, vehicles incorporate a halogen such as one or more fluorine atoms. In some specific instances, a vehicle is a perfluoro ether. In some particular instances, a vehicle is methoxynonafluorobutane or ethoxynonafluorobutane available from 3M Specialty Materials, St. Paul, MN. An organic polyhalogenic vehicle is optionally used as a substitute for a portion of a carrier in a composition. A vehicle optionally has a boiling point less than 78 °C. Optionally, a vehicle has a boiling point below 65 °C. A vehicle is optionally present at a final concentration of about 5 percent to 40 percent w/w. Optionally, a vehicle is present at from 15 percent to 25 percent w/w. Optionally, a vehicle is present at 20% w/w. It is appreciated that more than one vehicle is optionally present in an inventive composition. Optionally, 2, 3, 4, 5, 6, or more vehicles are present in an inventive composition.
- 20 [0032] Some embodiments of a composition are free of a vehicle. Optionally, a composition is free of an organic polyhalogenic vehicle.
- 25 [0033] A composition includes one or more non-volatile solvents that are suitable to solubilize a bioactive agent at a desired concentration. A non-volatile solvent is typically non-volatile at ambient temperatures and pressures on the surface of the skin. Illustrative examples of non-volatile solvents include but are not limited to dimethylisobutylol, ethoxydiglycol,
- 30

glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine, tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, benzoic acid, butyl alcohol, dibutyl sebecate, diglycerides, dipropylene glycol, eugenol, fatty acids, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid

5 surfactants, triethyl citrate, 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil,

10 cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, diethylene glycol monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugarsm ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum,

15 phenol, pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil, vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-(octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, cetareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG fatty acid esters, PEG-stearate, PEG-oleate,

20 PEG laurate, PEG fatty acid diesters, PEG-dioleate, PEG-distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid esters, PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate, hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil, PEG-octyl phenyl ether, PEG-alkyl ethers, PEG-cetyl ether, PEG-stearyl ether, PEG-sorbitan fatty acid

25 esters, PEG-sorbitan diisostearate, PEG-sorbitan monostearate, propylene glycol fatty acid esters, propylene glycol stearate, propylene glycol, caprylate/caprates, sodium pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolized C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl sulfoxide, azone and related

30 compounds, dimethylformamide, N-methyl formamide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2 myreth 10-adipate, honeyquat,

sodium pyroglutamic acid, abyssinica oil, dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol, PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone, hydrolyzed wheat protein, and combinations thereof.

5 [0034] The relative amounts of the non-volatile solvent and bioactive agent are dependent on the identity of the bioactive agent and the solvent. Optionally, the ratio of bioactive agent to non-volatile solvent is anywhere from 0.0001:1 to 1:1, or any value or range therebetween. Optionally, the ratio of bioactive agent to non-volatile solvent is from 0.01:1 to 0.1:1. Optionally, the ratio of bioactive agent to non-volatile solvent is from 0.02:1 to 0.2:1.

10 [0035] The relative amounts of non-volatile solvent and carrier varies depending on the exact amount of bioactive agent in the system. The ratios of the bioactive agent, non-volatile solvent(s), and carrier(s) is designed to provide a system such that the concentration of the bioactive agent is increased, optionally to a supersaturated level in the non-volatile solvent, upon vaporization of the carrier when the product is applied to the skin. In some embodiments, the composition includes a bioactive agent that is entirely in microcrystalline form, but is present at
15 a level relative to the amount of non-volatile solvent that it will redissolve to the molecular form upon volatilization of the carrier. Thus, the relative ratios of the bioactive agent, the carrier and the non-volatile solvent create a system that promotes effective administration or exposure of the bioactive agent to the subject.

[0036] In some embodiments, the ratios of the bioactive agent, non-volatile solvent(s), and
20 carrier(s) are designed to hold the bioactive agent just beyond or near the point of saturation prior to exposure to the air upon application to the skin or preparation for application to the skin or other use. The presence of the carrier in which the bioactive agent is not-soluble in the formulation of the composition prevents full solubilization of the bioactive agent. Upon exposure to the atmosphere or contact with the skin, the carrier evaporates promoting
25 solubilization of the microcrystalline form of the bioactive agent in the non-volatile solvent that surprisingly drives effective administration of the bioactive agent to the subject. Thus, the relative ratios of the bioactive agent, the carrier and the non-volatile solvent create a system that promotes effective administration or exposure of the bioactive agent to the subject. It is appreciated that the relative amounts of bioactive agent, the carrier and the non-volatile solvent
30 are readily appreciated by one of ordinary skill in the art. It is further appreciated that upon volatilization of the carrier the resulting formulation optionally does not form a solid, but remains in a lotion, cream, or other fluid form for ease of application to the skin as well as for optimal exposure of the bioactive agent to the skin.

[0037] In some embodiments, a bioactive agent is halobetasol in an amount from 0.001 to 1.0% by weight, or any value or range therebetween. Optionally, halobetasol is present in an amount ranging from 0.025 to 0.5% by weight. Optionally, halobetasol is present at 0.05% by weight.

5 [0038] In some embodiments, a bioactive agent is a vitamin A derivative such as a retinoid. As an example, some embodiments include hydroxyanastil retinoate, a form of all-trans retinoate sold by Concert, LLC, Memphis, TN, optionally in an amount of 0.1 percent by weight. This material is insoluble at this concentration in the carrier sold under the tradename GRANSIL
10 GTS, which is a mixture of ethyl trisiloxane and polysilicone-11. However, addition of the non-volatile solvent dimethyl isosorbide at 0.8% places the retinoate in a mixed state of solubilized material and crystalline material. Upon exposure to the environment for application to the skin, the carrier volatilizes allowing the crystalline retinoate to resolubilize in the solvent for increased penetration of the skin.

[0039] The inventive composition optionally includes other additives or pharmaceutical
15 carriers illustratively including: stabilizers such as the anti-oxidant BHT; surfactants illustratively Laureth-4; anti-oxidants illustratively vitamins C and E, and Green tea extract (i.e. *Camellia sinensis*) or SILOX GT from Collaborative Labs, Stony Brook, NY; and emollients illustratively the mixture or single components of the emollient sold under the brand name SYMREPAIR available from Symrise, Teterboro, NJ. One of ordinary skill in the art readily
20 appreciates additives suitable for use with the present invention such as to provide desired flow characteristics, absorption, evaporation, delivery of active agent, conversion of a prodrug, or other desired characteristic.

[0040] The compositions of the invention are also optionally diluted to the appropriate
25 bioactive agent level for application by using other topically acceptable compounds or vehicles which are optionally miscible with the bioactive agent(s) of the inventive compositions. Other cosmetic additives are optionally employed, either in the compositions of the invention or in those compositions when diluted with a suitable vehicle.

[0041] A composition optionally includes one or more thickeners. Illustrative examples of
30 thickeners include dimethicone crosspolymers such as dimethicone/vinyl dimethicone crosspolymer and dimethicone/phenyl vinyl dimethicone crosspolymers, high molecular-weight silicone waxes, acrylic polymers that are soluble in silicones, and other thickeners known in the

art that are soluble in a carrier. Illustrative examples of a thickener include polysilicone-11, and stearoxymethicone/dimethicone copolymer.

[0042] A composition optionally includes one or more opacifying agents. An opacifying agent is any agent known in the art compatible with the other components of a composition. Illustrative examples of opacifying agent include water-insoluble surface-active substances and polyoxyalkylene ethers, polymers and copolymers of styrene. Specific non-limiting examples of an opacifying agent include: titanium dioxide; aluminum caprylate; aluminum hydroxide hydrate; aluminum tristearate; attapulgit; calcium carbonate; calcium silicate; calcium sulfate; cellulose microcrystalline; cetyl alcohol; diatomaceous earth; dicalcium phosphate; glycol distearate; ethylene glycol distearate; iron powder; kaolin; magnesium carbonate; magnesium myristate; magnesium oxide; magnesium palmitate; magnesium silicate; (Z)-oleyl alcohol; petrolatum wax microcrystalline; polymethyl silsesquioxane; propylene glycol stearate; sasa senanensis leaf powder; silica; sodium polymethacrylate; solum fullonum; stearyl alcohol; talc powder; tricalcium phosphate; trimagnesium phosphate; zinc carbonate; zinc ricinoleate; opacifying agents listed in U.S. Patent No. 4,009,139; and combinations thereof.

[0043] The compositions formulated as described herein are optionally topically applied to the skin at a concentration that results in application of a bioactive agent at a desired concentration following volatilization of the carrier. Illustratively, a composition optionally includes 0.005 to 1.0 weight percent retinol, optionally 0.01 to 0.50 weight percent. A bioactive agent is optionally supersaturated upon evaporation of the carrier. Thus, the maximum amount of active agent is limited only by the ability to provide a supersaturated solution created upon application.

[0044] An active agent is optionally applied in the areas where fine lines, wrinkles, dry or inelastic skin or large pores are observed as a condition. Optionally, a moisturizer is applied with or after application of the inventive compositions to enhance the tactile comfort associated with application of the compositions and to enhance the desired therapeutic outcome such as musculoskeletal pain reduction, wrinkle effacement, or other benefits achieved by the compositions. An improved characteristic of the inventive composition is that the use of additional moisturizers is not essential. As such, an inventive composition is optionally free of an additional moisturizer.

- [0045] One or more moisturizers that are compatible with the carrier to a level of up to 35% by weight of the final formulation are optionally included. In some embodiments, a composition does not include a moisturizer. Moisturizers illustratively include petrolatum, ethylhexyl palmitate, cholesterol fatty acid ceramide, and squalene. The addition of one or more moisturizers is beneficial when the inventive composition is applied to previously dried skin or under conditions where dryness commonly occurs such as in cold climates, or winter months. Optionally, a moisturizing component is applied where the active agent itself has a drying effect such as when retinol or 5-fluorouracil is applied.
- [0046] With daily application of a retinol containing composition, skin texture, color and tone will improve. Wrinkles and fine lines will be reduced with minimal irritant effects.
- [0047] An inventive composition is optionally applied to the skin of a subject. A subject is optionally a patient. A subject is optionally a mammal such as humans, non-human primates, horses, goats, cows, sheep, pigs, dogs, cats, and rodents.
- [0048] An inventive composition is optionally provided as a lotion, cream, gel, bar, ointment, or in pad form. Optionally, the composition is provided in a single use container the contents of which are applied directly to the stratum corneum of a subject or applied to an applicator pad for subsequent delivery to the subject.
- [0049] A cooling effect is optionally observed upon topical application of the inventive composition. Cooling effect as used herein means reducing the temperature of skin, optionally, from about 1 to about 2°C upon application. The cooling effect includes the effect that results from carrier or vehicle evaporation.
- [0050] The inventive composition is optionally administered one to three times daily. Optionally, the inventive composition is administered once daily. Optionally, the inventive composition is administered weekly, biweekly, monthly, or any subdivision thereof. It is appreciated that the inventive composition is optionally administered for an amount of time suitable for efficacy of the active agent. Optionally, the inventive composition is administered for one to six weeks. Optionally, the inventive composition is administered indefinitely.
- [0051] Numerous skin or systemic conditions are treatable, diagnosable, or preventable with the inventive compositions illustratively including acne, wrinkles, musculoskeletal pain, inflammation, dryness, eczema, psoriasis, actinic and nonactinic keratoses, rosaceous, among others, or combinations thereof. U.S. Pat. No. 3,932,665 describes retinal as a therapeutic agent in a method for treating acne by topical application. The topical administration of 5-fluorouracil

for treatment of keratoses is described in U.S. Pat. No. 4,034,114. The inventive composition reduces the associated side effects that typically accompany topical or ophthalmologic administration of bioactive agents.

[0052] The inventive compositions are suitable for topical delivery of a bioactive agent to a subject optionally for the treatment of a skin condition. A skin condition is optionally treated by topically administering a composition to a subject with a condition or at risk for a condition such that the administering ameliorates or prevents the skin condition. With continued and regular use, a skin condition may be eliminated or prevented. Optionally, a composition is administered once to ameliorate, eliminate, or prevent a skin condition of a subject.

[0053] The inventive compositions optionally include a bioactive agent formulated in a carrier containing volatile silicone. With such a carrier, bioactive agent levels needed to achieve beneficial effects are minimized and the potential for irritant effects to the skin by a bioactive agent are greatly diminished.

[0054] Also provided are processes of storing one or more bioactive agents for subsequent topical administration to a subject or portion thereof. A process includes dissolving a bioactive agent in a non-volatile solvent and combining a carrier with the bioactive agent containing solvent. The presence of the carrier forces at least a portion, but less than 100% of the bioactive agent in a crystalline state.

[0055] The step of dissolving is by any method known in the art such as by stirring, vortexing, use of a physical mixing apparatus, or other known method. A solvent is optionally heated above room temperature for effective and complete solubilization of the bioactive agent. The amount of heat added is limited only by the stability of the components of the composition.

[0056] A process for storing one or more bioactive agents optionally includes the step of adding a thickener to the composition. A thickener is optionally added prior to dissolving a bioactive agent or subsequent thereto. Optionally, a thickener is added following combining a carrier with the solvent. The addition of a thickener creates a smooth, cream appearance and consistency to the composition.

[0057] One or more bioactive agents are optionally stored in the compositions in a state that is less than 100% in solution with the proviso that at least a portion of the bioactive agent is in a molecular state (i.e. solubilized). In a composition for storage of a bioactive agent or otherwise, a bioactive agent is optionally greater than 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent in molecular form.

[0058] A composition for storing one or more bioactive agents is optionally placed in an inert atmosphere. The term “inert” is appreciated to mean that the atmosphere or component thereof will not react with a bioactive agent. Illustrative examples of an inert atmosphere include nitrogen, argon, neon, or other inert gas known in the art.

5 [0059] A composition is optionally placed in a container that is opaque such that the composition is kept in minimal light conditions.

[0060] Various aspects of the present invention are illustrated by the following non-limiting examples. The examples are for illustrative purposes and are not a limitation on any practice of the present invention. It will be understood that variations and modifications can be made
10 without departing from the spirit and scope of the invention.

Example 1:

[0061] A retinoid delivery composition is formulated to include the following ingredients as listed in Table 1 as Formula A.

Table 1: Formula A

<u>Ingredient (INCI name / Brand name)</u>	<u>%w/w (final)</u>	<u>Supplier</u>
Phase A		
Diethyl sebacate	2.4	Ivanhoe Industries
Dimethyl isosorbide / Arlasolve DMI	0.8	Croda
Hydroxyananasatil retinoate/ MDI 403	0.1	Concert LLC
Phase B		
Diethyl sebacate	2	Ivanhoe Industries
Tetrahexyldecyl ascorbate / BV-OSC	1	Barnet
Tocopherol USP	0.5	DSM
Laureth-4 / Brij 30	0.5	Croda
Phase C		
Ethyl Trisiloxane (and) Polysilicone-11 /Gransil GTS	92.7	Grant Industries

15 [0062] To form the retinoid delivery composition of Table 1, the following process is preformed at standard temperature (approx. 25°C) and pressure (1 atm) in the absence of any heating or cooling. A suitably sized kettle is loaded with Phase A ingredients in the order shown in Table 1. These are propeller mixed (non-vortex) to dissolve all ingredients and create a clear

solution. Each Phase B ingredient is added to Phase A and mixed until completely dissolved. Separately, the Phase C ingredient is loaded into a suitably sized Kettle (Main Batch). The Phase A+B is slowly added to Phase C at a rate no faster than 5% of the weight of A+B per minute. The composition is mixed until uniform with slow side-sweep agitation. Mixing is stopped when a homogeneous gel is obtained. The composition is protected from light by transfer to a suitably sized container with a polyethylene liner.

[0063] Retinoid is present in the final formula partly in solution and partly in the form of microcrystals suspended in the silicone elastomer gel. Microcrystals form immediately after compounding because retinoid solubility in Phase A+B+C is less than in Phase A+B. This creates a haze. After product application to the skin surface, evaporation of the volatile silicone portion of the vehicle causes the microcrystalline retinoid to redissolve in the non-volatile portion of the vehicle remaining on the skin surface.

[0064] The composition is tested for contamination and physical properties as shown in Table 2.

Table 2:

<u>Property</u>	<u>Result</u>
Appearance:	Translucent pale Yellow Gel
Odor:	Mild characteristic
Non-Volatile matter wt.% (105°C, 3 hrs, 1.5 g, gravity oven)	14.7 - 16.1
pH:	n/a (anhydrous)
Viscosity: (200,000 - 250,000 cPs Apparatus: Brookfield DV-I+, Spindle T-E, 0.3 rpm, 1.0 min)	To match sample
Microbial Testing:	
Total Plate Count	NMT 100/gram
<i>Salmonella spp.</i>	Negative
<i>E. coli</i>	Negative
<i>S. aureus</i>	Negative
<i>A. niger</i>	Negative
Total yeast & molds	NMT 100/gram

Example 2:

[0065] The composition of Example 1 is reformed with varying concentrations of retinoid by also adjusting the relative concentration of Ethyl Trisiloxane and Polysilicone-11. The resulting compositions are listed in Table 3:

5 **Table 3:**

Formula	Retinoid (% w/w)
B	0.005
C	0.01
D	1.0

Example 3:

[0066] A corticosteroid containing composition is formed as in Table 4 as per Formula E.

[0067] **Table 4: Formula E**

<u>Ingredient (INCI name / Brand name)</u>	<u>%w/w (final)</u>	<u>Supplier</u>
Phase A		
Exoxydiglycol/Transcutol	2.0	Gattefosse
Halobetasol propionate	0.05	-
Phase B		
PPG-3 Benzyl ether myristate/ Crodamol STS	2.5	Croda
Titanium dioxide (and) Triethoxy caprylsilane/BDT-11S2	0.3	Kobo Products
Phase C		
Cyclopentasiloxane (and) Petrolatum (and) Stearoxymethicone/Dimethicone Copolymer (and) Dimethicone / Gransil GI CD-10P	85.15	Grant Industries
Dimethicone (and) Polysilicone-11 (and) Petrolatum / Gransil DMG-20P	10.0	Grant Industries

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[0068] To form the halobetasol composition of Formula E, the following process is preformed at standard temperature (approx. 25°C) and pressure (1 atm) in the absence of any heating or cooling. A suitably sized kettle is loaded with Phase A ingredients in the order shown in Table 4. These are propeller mixed (non-vortex) to dissolve all ingredients and create a clear solution. In a separate kettle, the Phase B ingredients are combined and propeller mixed (non-

15

vortex) to create a uniform dispersion. The Phase A and Phase B are then combined with continuous non-vortex mixing. Separately, the Phase C ingredients are loaded into a suitably sized kettle and blended with a slow, side-sweep mixing until uniform. The Phase A+B is slowly added to Phase C at a rate no faster than 5% of the weight of A+B per minute. The composition is mixed until uniform with slow side-sweep agitation. Mixing is stopped when a homogeneous cream is obtained. The composition is transferred to a suitably sized container for storage.

[0069] The composition is tested for contamination and physical properties as shown in Table 5.

Table 5:

<u>Property</u>	<u>Result</u>
Appearance:	Glossy, white soft cream
Odor:	Mild characteristic
Non-Volatile matter wt. % (105°C, 3 hrs, 1.5 g, gravity oven)	34.0 – 38.0
pH:	n/a (anhydrous)
Viscosity: (200,000 - 250,000 cPs Apparatus: Brookfield DV-II+, Spindle T-E, 0.3 rpm, 1.0 min)	To match sample
Microbial Testing:	
Total Plate Count	NMT 100/gram
<i>Salmonella spp.</i>	Negative
<i>E. Coli</i>	Negative
<i>S. Aureus</i>	Negative
<i>A. Niger</i>	Negative
Total yeast & molds	NMT 100/gram

Example 4:

[0070] The formula of Example 3 is adjusted with varying concentrations of halobetasol. The relative amounts of Phase C ingredients are adjusted to form 100% w/w depending on the desired amount of halobetasol. The following formulas are created.

Table 6:

Formula	Halobetasol (% w/w)
F	0.025
G	0.01
H	0.03

Example 5:

[0071] A topical anesthetic containing composition is formed as in Table 7 as per Formula I.

Table 7: Formula I

<u>Ingredient (INCI name / Brand name)</u>	<u>%w/w</u>	
	<u>(final)</u>	<u>Supplier</u>
Phase A		
Exoxydiglycol/Transcutol	2.0	Gattefosse
lidocane	4.0	-
Phase B		
PPG-3 Benzyl ether myristate/ Crodamol STS	2.5	Croda
Titanium dioxide (and) Triethoxy caprylsilane/BDT-11S2	0.3	Kobo Products
Phase C		
Cyclopentasiloxane (and) Petrolatum (and) Stearoxymethicone/Dimethicone Copolymer (and) Dimethicone / Gransil GI CD-10P	81.2	Grant Industries
Dimethicone (and) Polysilicone-11 (and) Petrolatum / Gransil DMG-20P	10.0	Grant Industries

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Example 6:

[0072] A corticosteroid containing composition is formed as in Table 8 as per Formula J.

Table 8: Formula J

<u>Ingredient (INCI name / Brand name)</u>	<u>%w/w</u>	
	<u>(final)</u>	<u>Supplier</u>
Phase A		
Exoxydiglycol/Transcutol	2.0	Gattefosse
Promoxine HCL (and) hydrocortisone (1% each)	2.0	-
Phase B		
PPG-3 Benzyl ether myristate/ Crodamol STS	2.5	Croda
Titanium dioxide (and) Triethoxy caprylsilane/BDT-11S2	0.3	Kobo Products

Phase C

Cyclopentasiloxane (and) Petrolatum (and) Stearoxymethicone/Dimethicone Copolymer (and) Dimethicone / Gransil GI CD-10P	83.2	Grant Industries
Dimethicone (and) Polysilicone-11 (and) Petrolatum / Gransil DMG-20P	10.0	Grant Industries

Example 7:

[0073] Patients presenting with acne to a dermatologist provide informed consent to a split face test comparing Formula A of Example 1 with a commercially available benzoyl peroxide topical acne treatment of equal active ingredient concentration (STRIDEX POWER PADS, Blistex, Inc. Oak Brook, IL).

[0074] Fifteen females aged 20 to 39 apply Formula A to one side of their faces and the benzoyl peroxide comparator to the other side once daily for two weeks. Each subject is asked to record any side effects such as dryness, irritation, and perceived skin clarification. Both the Formula A and the comparator demonstrate similar skin clarification. Subjects report less irritation and improved skin condition on the Formula A treated side relative to comparator.

Example 8:

[0075] A split face test is performed by using Formula A or a comparator as follows. Twelve females aged 20 to 59 apply Formula A to one side of their faces and comparator to the other side once daily for eight weeks. The comparator is made containing 46.3% Cyclomethicone-Tetramer; 35 % Alcohol SD 40B Anhydrous; 5% Ethylhexyl Palmitate; 5% Octyl Dimethyl PABA; 2% Benzophenone-3; 2% Demineralized Water; 2% Neopentyl Glycol Dicaprate; 1.5% Ethyl Cellulose K5000; 0.22% Butylated Hydroxytoluene; and 1% Retinoid Blend. The comparator is prepared essentially as described in U.S. Patent No. 4,826,828.

[0076] Thin shavings of the skin on each side of the face are taken before the test begins and after the eight week test period. The skin shavings after the test are in better condition than those before the test in all twelve women in the Formula A group and in nine of the twelve women in the comparator group. The skin of all women is both thicker and more organized after the test than before. All women in the Formula A group report improved moisture in the tested skin whereas the comparator group issues complaints of drying and cracking of the tested skin areas.

Example 9:

[0077] A split face test is performed by using Formula A or the comparator of Example 5 as follows. Twelve females aged 20 to 59 apply Formula A to one side of their faces and comparator to the other side once daily for eight weeks. Thin shavings of the skin on each side of the face are taken before the test begins and after the eight week test period. The skin shavings after the test are in better condition than those before the test in all twelve women in the Formula A group and in nine of the twelve women in the comparator group. The skin of all women is both thicker and more organized after the test than before. All women in the Formula A group report improved moisture in the tested skin whereas the comparator group issues complaints of drying and cracking of the tested skin areas.

Example 10:

[0078] Ten patients of varying ages ranging from 10 to 17 years, each diagnosed with atopic dermatitis have informed parental consent to have the composition of Formula E applied topically. Subjects present with moderate pruritus daily, extensive erythema, excoriation and induration/papulation on extremities. The composition of Formula E is topically applied once daily for two weeks. Subjects report reduction in itching and reduction in erythema within two days.

Example 11:

[0079] Twelve subjects each presenting with 3-5 acute acne lesions on the face are used to determine the effectiveness of Formulas E-H (three subjects per formula). A selected patch of effected skin is used for the placement of a circular patch of sufficient dimension to cover the lesion of one of Formulas A-H. The selected formulation is applied one to two times per day on the selected lesions. Each treatment site is evaluated after 4, 8 and 24 hours by a clinician to evaluate the lesion/pimple redness (erythema). The conditions of each of the affected areas with applied halobetasol containing formula are alleviated.

[0080] Various modifications of the present invention, in addition to those shown and described herein, will be apparent to those skilled in the art of the above description. Such modifications are also intended to fall within the scope of the appended claims.

[0081] It is appreciated that all reagents are obtainable by sources known in the art unless otherwise specified.

[0082] Patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are incorporated herein by reference to the same extent as if each individual application or publication was specifically and individually incorporated herein by reference.

- 5 [0083] The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

CLAIMS

1. A composition for topical delivery of a bioactive agent to a subject comprising:
a bioactive agent;
a non-volatile solvent into which said bioactive agent is soluble;
5 a carrier; and
a thickener.
2. The composition of claim 1 wherein said bioactive agent is a vitamin A derivative, corticosteroid, hydroxy acid, antimicrobial, anti-inflammatory, or a combination
10 thereof.
3. The composition of claim 2 wherein said vitamin A derivative is a retinoid.
4. The composition of claims 1 or 3 wherein said bioactive agent is hydroxyanastil
15 retinoate.
5. The composition of claims 1 or 2 wherein said carrier is a silicone that is volatile at standard temperature and pressure.
- 20 6. The composition of claims 1 or 2 wherein said bioactive agent is less than 100% in solution.
7. The composition of claims 1 or 2 wherein said bioactive agent is a corticosteroid.
- 25 8. The composition of claims 1 or 2 wherein said bioactive agent is halobetasol.
9. The composition of claim 8 wherein said halobetasol is present at 0.025 to 0.05 percent by weight.
- 30 10. The composition of claims 1 or 2 wherein said solvent is dimethylisobutyl alcohol, ethoxydiglycol, or a combination thereof.
11. The composition of claims 1 or 2 further including an opacifier.

12. The composition of claim 11 wherein said opacifier is titanium dioxide.
13. The composition of claims 1 or 2 wherein at least a portion of said bioactive agent
5 is in a crystalline state.
14. The composition of claims 1 or 2 wherein said bioactive agent is insoluble in said carrier.
- 10 15. A process of forming a composition comprising:
dissolving a bioactive agent in a non-volatile solvent;
combining a carrier with said solvent following said step of dissolving, the presence of
said carrier placing at least a portion of said bioactive agent in a crystalline state.
- 15 16. The process of claim 15 further comprising adding a thickener to said carrier.
17. The process of claim 15 wherein said adding creates a white cream.
18. The process of claims 15 or 16 wherein said bioactive agent is a vitamin A
20 derivative, corticosteroid, hydroxy acid, antimicrobial, anti-inflammatory, or a combination
thereof.
19. The process of claims 15 or 16 wherein said solvent is dimethylisosorbide,
ethoxydiglycol, or a combination thereof.
- 25 20. A process of treating a skin condition comprising:
administering the composition of claims 1 or 2 to a subject with a skin condition.
21. The process of claim 20 wherein said administering is topically.
- 30 22. The process of claim 20 wherein said administering is from one to three times
daily.

23. The process of claim 20 wherein said skin condition is acne, wrinkles, musculoskeletal pain, inflammation, dryness, eczema, psoriasis, actinic keratoses, nonactinic keratoses, or rosaceous.

5 24. The process of claim 20 wherein said skin condition is inflammation and said bioactive agent is halobetasol.

25. The process of claim 20 wherein said skin condition is wrinkles and said bioactive agent is vitamin A or a derivative thereof.

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26. The process of claim 20 wherein said skin condition is acne and said bioactive agent is vitamin A or a derivative thereof.

15 27. A use of the composition of claim 1 for preparation of a composition for treating a skin condition of a subject.

28. A composition substantially as described in any of the examples.

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治疗银屑病的复方外用药物 CN 1528313 A

ABSTRACT

本发明涉及一种治疗银屑病的复方外用药物。其特征在于：复方外用药物的基质载体中含有下列有效活性成分(重量百分比)：他扎罗汀0.025~0.1%，皮质激素0.01~0.2%。本发明的优点在于：他扎罗汀对受体选择性作用靶位明确，稳定性改善，局部应用主要存留于皮肤，代谢迅速，几乎不经皮透入系统中，局部皮肤刺激性相对较轻，几无全身不良反应。他扎罗汀与皮质激素合用在药效上有很强的互补和协同作用，不良反应可以抵消。

DESCRIPTION

治疗银屑病的复方外用药物

技术领域

：本发明涉及一种治疗银屑病的外用药物，尤其是一种治疗银屑病的复方外用药物。

背景技术

：银屑病是多基因及基因多态性遗传背景的T细胞介导的免疫性炎症疾病，发病机制非常复杂。活化的T细胞、炎症细胞与以角质形成细胞为主的皮肤组织细胞相互作用，形成全身及皮肤局部一系列表现和各临床亚型，银屑病的治疗问题一直是国内外皮肤病学研究的难点和热点。

银屑病药物治疗现状和现有的药物的治疗作用都是只能针对银屑病复杂的发病机制环节中的一部分，新药和新制剂的研制及临床治疗学的努力长期以来无质的突破，只能在利弊比率上作出调整，其对策包括：1.研制靶向性、选择性高的新药；2.研究联合疗法，顺序疗法和交替疗法的治疗新方案；3.合理选择或兼用系统和局部药物；4.优化外用复方制剂。目的皆为增强疗效和减轻不良反应。目前，此类药物都受本身固有 Toxicity 及选择性的制约，因而疗效有限，不良反应几不可免，疾病的多基因遗传本质及药物治疗不能解决复发问题，使患者需要长期、反复、乃至终身的治疗。

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：本发明的目的在于：针对治疗银屑病的常规治疗方法中存在的问题，提供一种新的治疗银屑病的复方外用药物。本发明是研制和优化新的局部外用复方制剂，旨在发展有特色的新药，能在一定程度上增强主药的疗效和减轻主药的不良反应，达到改善目前银屑病的治疗方法现状。

本发明的目的是这样实现的：一种治疗银屑病的复方外用药物，其特征在于：复方外用药物的基质载体中含有下列有效活性成分(重量百分比)：他扎罗汀0.025~0.1%，皮质激素0.01~0.2%。

本发明的优点在于：他扎罗汀是第三代维A酸类药物，是皮肤局部应用的维A酸，与第一代维A酸相比，具有受体选择性作用靶位明确，稳定性改善，局部应用主要存留于皮肤，代谢迅速，几乎不经皮透入系统中，局部皮肤刺激性相对较轻，几无全身不良反应。目前已证明，其单独局部外用治疗斑块型银屑病有效，而第一代维A酸单独应用效果较差，其药效作用包括调节角质形成细胞分化，抗增殖，和抗炎作用。

皮质激素局部治疗银屑病一般应用超强效、强效类，其机制是抑制上皮细胞增殖、抑制局部浸润的T细胞活性、抑制单核-巨噬细胞、成纤维细胞、血管内皮细胞及炎症细胞表达的异常细胞因子、粘附分子、炎症介质、趋化因子，从而抑制炎症。

他扎罗汀与皮质激素合用在药效上有很强的互补和协同作用，使针对银屑病病理环节的靶点扩大和增强，从而增强临床疗效。

此外他扎罗汀外用可引起一定的皮肤刺激性炎症，而皮质激素长期外用可引起皮肤萎缩。而他扎罗汀有抗皮肤萎缩作用，皮

Publication number	CN1528313 A
Publication type	Application
Application number	CN 03158379
Publication date	Sep 15, 2004
Filing date	Sep 29, 2003
Priority date	Sep 29, 2003
Also published as	CN1210035C
Inventors	郑家桐, 张崇璠, 李新宇, 陈汉, 高纪伟, 唐美育, 徐世芳
Applicant	中国医学科学院皮肤病研究所
Export Citation	BioTeX, EndNote, RefMan
Referenced by (2), Classifications (5), Legal Events (3)	
External Links: SIPO, Espacenet	

CLAIMS (3)

1.一种治疗银屑病的复方外用药物，其特征在于：复方外用药物的基质载体中含有下列有效活性成分(重量百分比)：他扎罗汀0.025~0.1%，皮质激素0.01~0.2%。

2.根据权利要求1所述的治疗银屑病的复方外用药物，其特征在于：所述的基质载体中含有的有效活性成分中的皮质激素及其含量为17.21-丙酮氯倍他索0.01~0.1%，或17.21-二氯松0.01~0.1%，或17-戊酸倍他米松0.05~0.2%，或17.21-二丙酸倍他米松0.01~0.1%，或去炎松0.05~0.2%，或17-丁酸氯倍他松0.01~0.1%。

3.根据权利要求1所述的治疗银屑病的复方外用药物，其特征在于：所述的复方外用药物含有的有效活性成分与基质载体混合后，形成软膏剂或乳膏剂。

质激素有抗炎作用，因而两药合用这两方面的不良反应可以抵消。

具体实施方式

：下面非限制性的例举了本发明涉及的部分实施例。

实施例1：本实施例的有效活性成分采用他扎罗汀0.1% (重量百分比，下同)和17-21-丙酸氯倍他索0.1%，基质载体采用液体石蜡、羊毛酯、乳化剂、抗氧化剂、乙醇、丙二醇和凡士林。

实施例2：本实施例的有效活性成分采用他扎罗汀0.025%和17-21-二氯拉松0.1%，基质载体采用液体石蜡、羊毛酯、乳化剂、抗氧化剂、乙醇、丙二醇和凡士林。

实施例3：本实施例的有效活性成分采用他扎罗汀0.1%和17-戊酸倍他米松0.2%，基质载体采用液体石蜡、羊毛酯、乳化剂、抗氧化剂、乙醇、丙二醇和凡士林。

实施例4：先将实施例1或实施例2或实施例3中的两种有效活性成分溶于总量5~10%的乙醇中待用；将总量5~10%的液体石蜡、总量8~15%的羊毛酯、适量的乳化剂、适量的抗氧化剂和凡士林混合加热至70℃；将总量10~20%的丙二醇加热至70℃后，加入液体石蜡、羊毛酯、乳化剂、抗氧化剂和凡士林的混合物搅拌均匀，待冷却至60℃时，加入已溶有两种有效活性成分的乙醇，最后用适量的凡士林调至药物总重量，再搅拌均匀形成软膏。

实施例5：本实施例的有效活性成分采用他扎罗汀0.05%和17-21-二丙酸倍氯米松0.05%，基质载体采用十六醇、凡士林、液体石蜡、单硬脂酸甘油酯、增溶剂、乳化剂、甘油、羟苯乙醇和蒸馏水。

实施例6：本实施例的有效活性成分采用他扎罗汀0.1%和去炎松0.1%，基质载体采用十六醇、凡士林、液体石蜡、单硬脂酸甘油酯、增溶剂、乳化剂、羟苯乙醇和蒸馏水。

实施例7：本实施例的有效活性成分采用他扎罗汀0.1%和17-丁酸氯倍他松0.1%，基质载体采用十六醇、凡士林、液体石蜡、单硬脂酸甘油酯、增溶剂、乳化剂、羟苯乙醇和蒸馏水。

实施例8：先将实施例5或实施例6或实施例7中的两种有效活性成分及0.1%的羟苯乙醇溶于增溶剂中；再将总量8~12%的十六醇、总量5~10%的凡士林、总量8~12%的液体石蜡、总量5~10%的单硬脂酸甘油酯及适量的乳化剂混合加热至80~85℃；将总量0.5~5%的甘油酯与适量的蒸馏水混合加热至80~85℃，并将其与上述十六醇、凡士林、液体石蜡、单硬脂酸甘油酯及乳化剂的混合物混合乳化；将乳化后的混合物离开热源，搅拌冷却至65℃时，加入溶有两种有效活性成分和羟苯乙醇的增溶剂，搅拌均匀形成乳膏剂。

REFERENCED BY

Citing Patent	Filing date	Publication date	Applicant	Title
EP2612865A1	Jan 9, 2012	Jul 10, 2013	Almirall S.A.	Topical pharmaceutical compositions comprising bexarotene and a corticosteroid
WO2013104399A1	Dec 18, 2012	Jul 18, 2013	Almirall, S.A.	Topical pharmaceutical compositions comprising bexarotene and a corticosteroid

CLASSIFICATIONS

International Classification A61K31/57, A61P17/06, A61K31/56, A61K38/35, A61K9/06

LEGAL EVENTS

Date	Code	Event	Description
Sep 15, 2004	C06	Publication	
Nov 17, 2004	C10	Request of examination as to substance	
Jul 13, 2005	C14	Granted	

Patents

Application

Grant

English

Chinese

Find prior art

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Complex external medicine for treating psoriasis

CN 1528313 A

ABSTRACT

The present invention relates to a compound medicine for external application for curing psoriasis. It is characterized by that in the matrix carrier of said compound medicine for external application are contained the following effective active components: (wt%) tazarotene 0.025-0.1% and cortical hormone 0.01-0.2%. Its therapeutic effect is good, and it has no adverse reaction.

DESCRIPTION translated from Chinese

Compound topical treatment of psoriasis

Technical Field

: The present invention relates to a method of treating psoriasis topical medications, especially for treating psoriasis topical compound.

Background

: Psoriasis is a multi-gene and gene polymorphism genetic background of T cell mediated autoimmune inflammatory disease pathogenesis is very complex. Activation of T cells, inflammatory cells and skin cells to keratinocytes-based interaction, forming a series of systemic and local skin manifestations and various clinical subtypes of psoriasis treatment has been the study of dermatology at home and abroad difficult and hot.

Status of drug treatment of psoriasis and treatment of existing drugs for psoriasis are only part of the complex pathogenesis part, and trying to develop new drugs and clinical studies of the new formulations have long no qualitative breakthrough, can make adjustments on the pros and cons ratio, their responses

Try the new Google Patents, with machine-classified Google Scholar results, and al choice or a combination of systems, and local drug 4 Optimizing topical compound preparation. Are all aim to enhance the efficacy and reduce the side effects. Currently, such drugs are subject to inherent toxicity and selective constraints, which limited efficacy, adverse reactions several non-free, multi-genetic nature of the disease and drug therapy can not solve recurring problems, so patients need long-term, repeated, or even a lifetime to drugs.

DISCLOSURE

: The purpose of the present invention is: for conventional treatments for psoriasis problems provide a new compound topical treatment of psoriasis. The present invention is to develop and optimize new topical compound, aimed at developing distinctive new drugs that can enhance the efficacy of the main drug and mitigate adverse effects of the main drug to a certain extent, to improve the status of the current method of treatment of psoriasis.

The purpose of the present invention is implemented as follows: a compound topical treatment of psoriasis, characterized by: Compound topical carrier matrix containing the following active component (wt%): tazarotene 0.025 to 0.1% corticosteroids 0.01 to 0.2%.

Advantage of the present invention is: tazarotene is a third generation Vitamin A acid drugs, is topically applied skin Vitamin A acid, compared with the first generation of Vitamin A acid, has the role of receptor selective target clear, stable improvement, topical application was remained in the skin, rapid metabolism, hardly transdermal penetration systems, local skin irritation are relatively mild, almost no body without adverse reaction. Has proved that its individual plaque psoriasis

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Application number	CN 03158379
Publication date	Sep 15, 2004
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Inventors	郑家桐, 张崇璠, 李新宇, 陈江, 高纪伟, 唐美育, 徐世芳
Applicant	中国医学科学院皮肤病研究所
Export Citation	BibTeX, EndNote, RefMan
Referenced by (2), Classifications (5), Legal Events (3)	
External Links: SIPO, Espacenet	

CLAIMS (3) translated from Chinese

A compound topical treatment of psoriasis, characterized by: Compound topical carrier matrix containing the following active component (wt%): 0.025% to 0.1% tazarotene, corticosteroids 0.01 to 0.2%.

The topical treatment of psoriasis compound according to claim 1, characterized in that: the active component of the matrix contained in the carrier and the content of corticosteroid clobetasol propionate 17.21-0.01 to 0.1%, or 17.21- diflorasone 0.01 to 0.1%, or 17- betamethasone valerate 0.05 to 0.2%, or 17.21- beclomethasone dipropionate 0.01% to 0.1%, or 0.05 to 0.2 triamcinolone %, or 17- butyrate clobetasone 0.01 to 0.1%.

3. The treatment of psoriasis topical compound according to claim, characterized in that: said compound after topical drugs containing effective active ingredient is mixed with a carrier matrix to form an ointment or cream.

topical treatment effective, and the first generation of poor Vitamin A acid alone effect, the pharmacodynamic effects including regulation of keratinocyte differentiation, antiproliferative, and anti-inflammatory effects.

Corticosteroids topical treatment of psoriasis general application of super-efficient, powerful class, their mechanism of inhibition of epithelial cell proliferation, inhibition of T cell activity of local infiltration, inhibit monocyte macrophages, fibroblasts, endothelial cells and inflammation abnormal expression of cytokines, adhesion molecules, inflammatory mediators, chemokines, thereby inhibiting inflammation.

Tazarotene and on the efficacy of corticosteroids in combination are highly complementary and synergy targets for the psoriasis pathology link so that expansion and enhancement, thereby enhancing clinical efficacy.

In addition tazarotene topical can cause some skin irritation inflammation, and long-term topical corticosteroids can cause skin atrophy. And tazarotene have anti-skin atrophy effect, corticosteroids have anti-inflammatory effect, therefore coadministration of adverse reactions in these two areas can be offset.

DETAILED DESCRIPTION

: The following non-limiting example of some embodiments of the present invention.

Example 1: effective active ingredient of the present embodiment employs Tazarotene 0.1% (percentage by weight, hereinafter the same) and 17,21- clobetasol propionate 0.1%, the carrier matrix using liquid paraffin, lanolin, emulsifiers, anti-oxygen agent, alcohol, propylene glycol, and petroleum jelly.

Example 2: effective active ingredient of the present embodiment employs tazarotene 0.025% and 0.1% 17,21- diflorasone, the carrier matrix using liquid paraffin, lanolin, emulsifiers, antioxidants, ethanol, propylene glycol and petrolatum.

Example 3: effective active ingredient of the present embodiment employs 0.1% tazarotene and betamethasone 17- valerate 0.2%, the carrier matrix using liquid paraffin, lanolin, emulsifiers, antioxidants, ethanol, propylene glycol and petrolatum.

Example 4: 1 or Example 2 or Example 3 was dissolved in the total amount of the two active ingredients effective implementation of the first embodiment of 5 to 10% ethanol and set aside; the total amount of 5 to 10% of liquid paraffin, total the amount of 8 to 15% lanolin, the amount of emulsifier, and an appropriate amount of antioxidant mixed petrolatum was heated to 70 °C; total amount 10 to 20% propylene glycol was heated to 70 °C, was added liquid paraffin, lanolin, emulsifying mixture, antioxidants and petrolatum stir, to be cooled to 60 °C, was added a solution of ethanol has two effective active ingredients, and finally with the right amount of Vaseline adjusted to the total weight of the drug, and then stir the formation of ointment.

Example 5: effective active ingredient of the present embodiment employs tazarotene 17,21- 0.05% and 0.05% bedomethasone dipropionate, the carrier matrix using cetyl alcohol, petrolatum, liquid paraffin, glyceryl monostearate, increasing solvents, emulsifiers, glycerin, ethylparaben and distilled water.

Example 6: effective active ingredient of the present embodiment employs tazarotene 0.1% and 0.1% triamcinolone, the carrier matrix using cetyl alcohol, petrolatum, liquid paraffin, glyceryl monostearate, solubilizers, emulsifiers, ethylparaben and distilled water.

Example 7: effective active ingredient of the present embodiment employs tazarotene 0.1% and 17- butyrate clobetasone 0.1%, the carrier matrix using cetyl alcohol, Vaseline, liquid paraffin, glyceryl stearate, increasing solvents, emulsifiers, ethylparaben and distilled water.

Example 8: Example 5 or Example 6 or Example 7 in both cases the effective active ingredients and 0.1% of ethylparaben were dissolved by a solvent first embodiment; then 8 to 12% of the total amount of cetyl alcohol, 5 to 10% of the total amount of petrolatum, 8 to 12% of the total amount of liquid paraffin, the total amount of emulsifier from 5 to 10% and the amount of glycerol monostearate was heated to 80 ~ 85 °C; will total 0.5 to 5% of the glycerides with a suitable amount of distilled water heated to 80 ~ 85 °C, and above cetyl alcohol, petrolatum, liquid paraffin, glyceryl monostearate and mixed emulsion emulsifier mixture; the emulsified When the mixture from heat, stirring cooling to 85 °C, added to a solution of two effective active ingredients and ethylparaben solubilizers, stir cream form.

REFERENCED BY

Citing Patent	Filing date	Publication date	Applicant	Title
EP2612665A1	Jan 9, 2012	Jul 10, 2013	Aimiral S.A.	Topical pharmaceutical compositions comprising bexarotene and a corticosteroide
WO2013104399A1	Dec 18, 2012	Jul 18, 2013	Aimiral, S.A.	Topical pharmaceutical compositions comprising bexarotene and a corticosteroids

CLASSIFICATIONS

9/14/2016

Patent CN1528313A - Complex external medicine for treating psoriasis - Google Patents

International Classification A61K31/57, A61P17/06, A61K31/56, A61K38/35, A61K9/08

LEGAL EVENTS

Date	Code	Event	Description
Sep 15, 2004	C06	Publication	
Nov 17, 2004	C10	Request of examination as to substance	
Jul 13, 2005	C14	Granted	

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 99336000292	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2018/032359	International filing date (<i>day/month/year</i>) 11 May 2018 (11-05-2018)	(Earliest) Priority Date (<i>day/month/year</i>) 12 May 2017 (12-05-2017)
Applicant VALEANT PHARMACEUTICALS NORTH AMERICA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/032359

A. CLASSIFICATION OF SUBJECT MATTER			
INV. A61K31/4436	A61K9/00	A61K47/14	A61K47/32
A61K9/107			
ADD.			
According to International Patent Classification (IPC) or to both national classification and IPC			

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols) A61K A61P
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/205001 A1 (VALEANT PHARMACEUTICALS NORTH AMERICA [US]) 22 December 2016 (2016-12-22)	1-12
Y	page 4, paragraph 0011 page 10, paragraph 0038 pages 15-16, paragraph 0050-0051 pages 18-19, paragraph 0055-0059; table 3 page 21; table 4 page 27; table 7	1-15
Y	----- CN 1 528 328 A (SKIN DISEASE INST CHINESE ACAD [CN]) 15 September 2004 (2004-09-15) abstract ----- -/--	1-15

☒ Further documents are listed in the continuation of Box C.	☒ See patent family 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 application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 17 July 2018	Date of mailing of the international search report 31/07/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Rodríguez-Palmero, M

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/032359

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KIRCIK LEON H: "Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris.", JOURNAL OF DRUGS IN DERMATOLOGY : JDD JUL 2009, vol. 8, no. 7, July 2009 (2009-07), pages 650-654, XP9506864, ISSN: 1545-9616 page 651, column 1, paragraph 2 figures 1-3	1-15
Y	----- SHALITA A R ET AL: "Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study.", CUTIS JUN 1999, vol. 63, no. 6, June 1999 (1999-06), pages 349-354, XP9506866, ISSN: 0011-4162 page 350, column 2, paragraph 2 figures 1-3 -----	1-15

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

page 2 of 2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/032359

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016205001 A1	22-12-2016	AU 2016279801 A1 CA 2988577 A1 CN 108282998 A EP 3310389 A1 KR 20180053292 A US 2016367570 A1 US 2018177803 A1 WO 2016205001 A1	04-01-2018 22-12-2016 13-07-2018 25-04-2018 21-05-2018 22-12-2016 28-06-2018 22-12-2016
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CN 1528328 A	15-09-2004	NONE	
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Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2018/032359

International filing date (day/month/year)
11.05.2018

Priority date (day/month/year)
12.05.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4436 A61K9/00 A61K47/14 A61K47/32 A61K9/107 A61P17/10

Applicant
VALEANT PHARMACEUTICALS NORTH AMERICA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Rodríguez-Palmero, M

Telephone No. +49 89 2399-0



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2018/032359

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2018/032359

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>11, 13-15</u>
	No: Claims	<u>1-10, 12</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Documents

- D1 WO 2016/205001 A1 (VALEANT PHARMACEUTICALS NORTH AMERICA [US]) 22 December 2016 (2016-12-22)
- D2 CN 1 528 328 A (SKIN DISEASE INST CHINESE ACAD [CN]) 15 September 2004 (2004-09-15)
- D3 KIRCIK LEON H: "Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris.", JOURNAL OF DRUGS IN DERMATOLOGY : JDD JUL 2009, vol. 8, no. 7, July 2009 (2009-07), pages 650-654, XP9506864
- D4 SHALITA A R ET AL: "Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study.", CUTIS JUN 1999, vol. 63, no. 6, June 1999 (1999-06), pages 349-354, XP9506866

- 1.1 A machine translation of D2 is attached to the present opinion.
- 1.2 Unless indicated, reference is made to the passages indicated in the international search report.

2 Patentability

Claims 12-15 are drafted as method of treatment claims, covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

An opinion on novelty/inventive step of these claims will be given based on the use-related composition defined therein.

3 Novelty (Art. 33(2) PCT)

D1 discloses that oil-in-water emulsions comprising tazarotene 0.045% either alone or in combination with halobesatol propionate are effective in the treatment of psoriasis. The components of the emulsions are identical to those of the present application.

Consequently, present claims 1-10, 12 are not novel over this document.

Claims 11, 13-15 are novel.

4 Inventive Step (Art. 33(3) PCT)

- 4.1 Present claim 11 concerns the formulation of the composition defined in claim 1 as a cream. D1 suggests that the compositions described therein can also be in the form of a cream (see p. 40-41, par. [0087]). Therefore, the subject-matter of present claim 11 is obvious in the light of D1 taken alone.

- 4.2 Present claims 13-15 concern compositions comprising tazarotene 0.045% for use in the treatment of acne.

D2-D4 disclose compositions comprising tazarotene for use in the treatment of acne:

D2 teaches compositions containing tazarotene 0.01-2% in the form of emulsifiable past or gel, liniment or film for use in the treatment of acne. Two compositions comprise tazarotene at 0.025% together with an antibiotic agent. See p. 3, par. 2 and examples 5 and 8 of the machine translated document.

D3 and D4 show that tazarotene 0.05% in the form of a cream or gel is effective and safe in the treatment of acne vulgaris.

D2-D4 are considered the closest prior art for the present claims 13-15.

The difference vs D2 is the formulation as an oil-in-water emulsion. The difference vs D3 and D4 is the concentration of tazarotene in the composition, which is defined in the claims to be "less than 0.05%".

However, none of these two differences is linked to a surprising effect: the person skilled in the art would expect that the compositions described in D2 would also be effective when formulated as oil-in-water emulsions. Also, the skilled person would expect that reducing the content of tazarotene from 0.05% (as in D3/D4) to 0.045% (in the present application) would not render the composition ineffective in the treatment of acne.

The problem is thus to provide an alternative to the compositions of D2-D4. The solution is to formulate tazarotene at less than 0.05% in an oil-in-water emulsion.

D1 would provide a guidance to formulate tazarotene compositions at the claimed concentrations as oil-in-water emulsions.

Consequently, the subject-matter of claims 13-15 is considered to be an obvious alternative in view of D2-D4 in combination with D1.

5 Industrial applicability (Art. 33(4) PCT)

Present claims 1-15 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 99336-000208	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2016/035991	International filing date (<i>day/month/year</i>) 6 June 2016 (06-06-2016)	(Earliest) Priority Date (<i>day/month/year</i>) 18 June 2015 (18-06-2015)
Applicant VALEANT PHARMACEUTICALS NORTH AMERICA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

TOPICAL COMPOSITIONS COMPRISING A CORTICOSTEROID AND A RETINOID FOR TREATING PSORIASIS

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/035991

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K45/06 A61K31/192 A61K31/573 A61K9/00 A61K47/14
A61K9/06 A61K47/44 A61P17/06

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/349981 A1 (EVERS FRITJOF [DE] ET AL) 27 November 2014 (2014-11-27) paragraphs [0026], [0027], [0030], [0074], [0139]; claims 1, 2, 6, 7; example 10; table 3 -----	1-30
X	LEBWOHL M ET AL: "Duration of improvement in psoriasis after treatment with tazarotene 0.1% gel plus clobetasol propionate 0.05% ointment: comparison of maintenance treatments.", INTERNATIONAL JOURNAL OF DERMATOLOGY JAN 2001, vol. 40, no. 1, January 2001 (2001-01), pages 64-66, XP009191230, ISSN: 0011-9059 abstract ----- -/-	1-30

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 August 2016

Date of mailing of the international search report

11/08/2016

Name and mailing address of the ISA/

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

Authorized officer

Ansaldo, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/035991

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DHAWAN SUNIL S ET AL: "Tazarotene cream (0.1%) in combination with betamethasone valerate foam (0.12%) for plaque-type psoriasis", JOURNAL OF DRUGS IN DERMATOLOGY, STRATEGIC COMMUNICATION IN DERMATOLOGY, NEW YORK, NY, US, vol. 4, no. 2, 1 March 2005 (2005-03-01), pages 228-230, XP009159245, ISSN: 1545-9616 abstract	1-30
X	----- US 2012/129824 A1 (ANGEL ARTURO [US] ET AL) 24 May 2012 (2012-05-24) the whole document -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/035991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014349981 A1	27-11-2014	AU 2012365658 A1 CA 2857207 A1 CL 2014001776 A1 CN 104053437 A CO 7000772 A2 CR 20140326 A EA 201400806 A1 EP 2802321 A1 HK 1198423 A1 JP 2015503573 A KR 20140107370 A PE 23752014 A1 PH 12014501573 A1 SG 11201403762P A US 2014349981 A1 WO 2013104399 A1 ZA 201403483 B	03-07-2014 18-07-2013 29-08-2014 17-09-2014 21-07-2014 16-01-2015 27-02-2015 19-11-2014 24-04-2015 02-02-2015 04-09-2014 11-01-2015 08-10-2014 30-07-2014 27-11-2014 18-07-2013 24-06-2015
US 2012129824 A1	24-05-2012	AU 2011345240 A1 CA 2817524 A1 CN 103228281 A EP 2643002 A1 JP 2013542990 A KR 20140043044 A NZ 610659 A RU 2013128607 A US 2012129824 A1 US 2014336161 A1 WO 2012087443 A1	30-05-2013 28-06-2012 31-07-2013 02-10-2013 28-11-2013 08-04-2014 29-05-2015 27-12-2014 24-05-2012 13-11-2014 28-06-2012

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2016/035991	International filing date (day/month/year) 06.06.2016	Priority date (day/month/year) 18.06.2015
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International Patent Classification (IPC) or both national classification and IPC
INV. A61K45/06 A61K31/192 A61K31/573 A61K9/00 A61K47/14 A61K9/06 A61K47/44 A61P17/06

Applicant
VALEANT PHARMACEUTICALS NORTH AMERICA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Ansaldo, M Telephone No. +49 89 2399-0 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/035991

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/035991

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-30</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-30</u>
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reference is made to the following documents:

- D1 US 2014/349981 A1 (EVERS FRITJOF [DE] ET AL) 27 November 2014
- D2 LEBWOHL M ET AL: "Duration of improvement in psoriasis after treatment with tazarotene 0.1% gel plus clobetasol propionate 0.05% ointment: comparison of maintenance treatments.", INTERNATIONAL JOURNAL OF DERMATOLOGY JAN 2001, vol. 40, no. 1, January 2001 (2001-01), pages 64-66, XP009191230
- D3 DHAWAN SUNIL S ET AL: "Tazarotene cream (0.1%) in combination with betamethasone valerate foam (0.12%) for plaque-type psoriasis", JOURNAL OF DRUGS IN DERMATOLOGY, STRATEGIC COMMUNICATION IN DERMATOLOGY, NEW YORK, NY, US, vol. 4, no. 2, 1 March 2005 (2005-03-01), pages 228-230, XP009159245
- D4 US 2012/129824 A1 (ANGEL ARTURO [US] ET AL) 24 May 2012

Unless otherwise specified, reference is made to the passages cited in the search report.

1. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Claims 15-30 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1 (iv) PCT

Patentability, in particular novelty and inventive step, of claims 15-30 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2. D1 discloses a topical composition comprising bexarotene and a corticosteroid, such as clobetasol, betamethasone, halobetasol, fluocinonide for the treatment of psoriasis.

The corticosteroid may be present in a concentration of less than 0.05 wt % and the bexarotene concentration is in the range of 0.1 wt. % to 2.0 wt. %.

In the footnote of table 3 D1 discloses that "different concentrations of tazarotene (from 0.05 to 0.2 wt. %) and betamethasone dipropionate (from 0.05 to 0.1 wt. %) were tested in the combination".

3. The subject-matter of the present application appears to be novel (Art. 33 (3) PCT) over D1 in view of the specific concentration of the retinoid of less than 0.09 wt %.

4. The object of the present application may be regarded as the provision of an alternative topical combination of corticosteroids and retinoids for the treatment of psoriasis.

5. The solution proposed by the present application is the selection of the specific concentration of the retinoid.

6. D1 clearly mentions concentrations of tazarotene below 0.09 wt%.

D2 discloses the use of tazarotene 0.1% gel plus clobetasol propionate 0.05 wt % ointment for the treatment of psoriasis. D2 also mentions on page 228, Ic, 1. par that tazarotene is available as cream or gel in concentrations of 0.05 wt%.

Therefore, in view of D1 and D2 the skilled person would have considered using retinoids at concentrations of less than 0.09% without the involvement any inventive activity.

Furthermore, the specific retinoid concentration of less than 0.09 wt. % appears to be an arbitrary selection since not linked to any unexpected technical effect.

In fact a selection can only be regarded as being inventive if it is a purposive selection and not an arbitrary one.

Unless the applicant can show that retinoids in a concentration of less than 0.09 wt % in combination with corticosteroids have a different and unexpected effect in respect to prior art compositions having a retinoid concentration of 0.1 wt % (see D2 and D3) no inventive merit for the present application may be acknowledged.

The limitation of the composition by specifying the type of carrier (i.e. by incorporating claims 7-14 into claim 1) would also not be considered inventive in view of D4 disclosing pharmaceutical compositions useful for treating skin disorder comprising corticosteroid e.g. clobetasol propionate at a concentration less than 0.05%, and a liquid oil component containing ester of monocarboxylic and dicarboxylic acids.

Re Item VIII

The relative terms DCAE and MCAE used in claims 9-10, 24-25 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

The same applies to the term "positive concentration" used in claims 1 and 15,

Electronic Patent Application Fee Transmittal				
Application Number:		16179576		
Filing Date:		02-Nov-2018		
Title of Invention:		TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		
First Named Inventor/Applicant Name:		Angel Arturo		
Filer:		Andrew James Anderson/Michelle Seifert		
Attorney Docket Number:		99336.000342		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description		Fee Code	Quantity	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 1 month with \$0 paid	1251	1	200	200
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
Total in USD (\$)				440

Electronic Acknowledgement Receipt	
EFS ID:	36638336
Application Number:	16179576
International Application Number:	
Confirmation Number:	1093
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Angel Arturo
Customer Number:	134756
Filer:	Andrew James Anderson/Michelle Seifert
Filer Authorized By:	Andrew James Anderson
Attorney Docket Number:	99336.000342
Receipt Date:	19-JUL-2019
Filing Date:	02-NOV-2018
Time Stamp:	14:49:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$440
RAM confirmation Number	072219INTEFSW00001130033875
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		99336-342_US_Response_due_July_20_2019.pdf	259096	yes	13
			3ca9c0934db297b4dbc2080adad524e26332c272		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		6	13	
	Claims		2	5	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	99336-342_IDS.pdf	1210156	no	5
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Warnings:					
Information:					
3	Foreign Reference	99336-293_FPD1_WO2016205001A1.pdf	1679775	no	52
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Warnings:					
Information:					
4	Foreign Reference	99336-293_FPD2_CN1528328A.pdf	361319	no	8
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Warnings:					
Information:					
5	Foreign Reference	99336-293_FPD2_CN1528328A-Translation.pdf	5980767	no	8
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Warnings:					
Information:					
6	Foreign Reference	99336-293_FPD3_2012087443.pdf	1163087	no	31
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Warnings:					
Information:					
7	Foreign Reference	99336-293_FDP4_2461MUM2009.pdf	1836830	no	31
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Warnings:					
Information:					
8	Foreign Reference	99336-293_FDP4_2461MUM2009-translation.pdf	44634	no	1
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Warnings:					
Information:					
9	Foreign Reference	99336-293_FDP5_2012061630.pdf	2815487	no	56
			559fa193e4c3eeb2dc9871f9350f15a04a3c87b5		
Warnings:					
Information:					
10	Foreign Reference	99336-293_FDP6_0047211.pdf	475337	no	12
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Warnings:					
Information:					
11	Foreign Reference	99336-293_FDP7_2004058262.pdf	1780317	no	38
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Warnings:					
Information:					
12	Foreign Reference	99336-293_FDP8_2012051614.pdf	1159643	no	25
			79e1ac7e2e013a3b08db6113f533f81ded2fa560		
Warnings:					
Information:					

13	Foreign Reference	99336-293_FDP9_CN1528313_with_translation.pdf	446556	no	5
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Warnings:					
Information:					
14	Non Patent Literature	99336-293_NPL1_ISR_WO.pdf	310431	no	10
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Warnings:					
Information:					
15	Non Patent Literature	99336-293_NPL2_Kircik.pdf	1663599	no	6
			353fb479527bafdd29bdd891a4a03f9d5e40a0e		
Warnings:					
Information:					
16	Non Patent Literature	99336-293_NPL3_Shalita_et_al.pdf	662350	no	6
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Warnings:					
Information:					
17	Non Patent Literature	99336-207_NPL4_Lebwohl.pdf	132751	no	7
			fee2e3ad73ecb17d9b4919eea40e3a4fc0cf72e2		
Warnings:					
Information:					
18	Non Patent Literature	99336-207_IDS_NPL5_Dhawan.pdf	4832185	no	3
			ec927d9407db67ba9a7f26814c4c6f53e17647a1		
Warnings:					
Information:					
19	Non Patent Literature	99336-207_NPL6_Tazorac.pdf	297701	no	13
			f6a460bc2d4b8556fdd1a3aaad42f96481a9e813		
Warnings:					
Information:					

20	Non Patent Literature	99336-293_NPL7_ISR_WO_8-2016.pdf	335037	no	10				
			675c8d1f9fc956c95d12d416f0fe8d8a320722d8						
Warnings:									
Information:									
21	Non Patent Literature	99336-293_NPL8_Hecker_et_al.pdf	289325	no	4				
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Warnings:									
Information:									
22	Fee Worksheet (SB06)	fee-info.pdf	32655	no	2				
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Warnings:									
Information:									
Total Files Size (in bytes):			27769038						
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.									

REMARKS

The Office action dated March 20, 2019 and the cited references have been carefully considered.

Claim 1 is amended to more particularly specify wherein the composition comprises a sole active pharmaceutical ingredient consisting of tazarotene or a pharmaceutically acceptable tazarotene acid salt at a concentration of 0.045 percent by weight (as supported, e.g., by original claims 3 and 5 and Table 2 of the specification), and is an oil-in-water emulsion (as supported, e.g., by original claims 4 and 6-9). Claims 2, 3, 5, and 13-23 have been cancelled. New claims 24-28 are added, supported, e.g., by Table 2 of the specification. No new matter has been added. Entry of the present amendment and reconsideration of the application are respectfully requested.

Status of the Claim

Claims 1-6, 12-15, and 20-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior[®] (Tazarotene) Foam 0.1% package insert (hereinafter referred to as “Fabior[®] 0.1%”).

Claims 8-11, 16, 18, and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1% in view of Singh et al. (Dosage Forms: Non-Parenteral in Encyclopedia of Pharmaceutical technology, 2002, Marcel Dekker; hereinafter referred to as “Singh”).

Claims 7 and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1% in view of Fiume et al. (*Int. J. Toxicol.* (2012 July-August), 31(4 Suppl.):5S-76S; hereinafter referred to as “Fiume”).

Claims 1-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of copending Application No. 15/977088.

Claims 1-23 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-23 of copending Application No. 16/179,561.

Applicant respectfully traverses these rejections for the reasons set forth below.

Rejection of claims 1-6, 12-15, and 20-23 under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1%

Claims 1-6, 12-15, and 20-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1%. Applicant respectfully traverses this rejection with respect to the present amended claims because Fabior[®] 0.1% does not teach or suggest all of the limitations of independent claims 1 and 28.

To demonstrate that a claim is obvious, the party asserting invalidity must present evidence that all limitations of the claim are present in the prior art. *Fresenius USA, Inc. v. Baxter Int'l, Inc.* 582 F.3d 1288, 1296 (Fed. Cir. 2009). See also *Ex parte Reed* (BPAI, Jul. 14, 2009, Slip op., p. 7) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)) (“To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.”). In addition, “[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.” MPEP § 2143.03 (9th Ed., Rev. 08.2017, Jan. 2018, p. 2100-235) (quoting *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)).

Nowhere in Fabior[®] 0.1% is there teaching or suggestion of a tazarotene oil-in-water emulsion or tazarotene concentration of 0.045% (less than half the concentration in Fabior[®] 0.1%), as recited in independent claims 1 and 28. Thus, Fabior[®] 0.1% does not teach or suggest all of the limitations of independent claim 1. Consequently, these claims are nonobvious over Fabior[®] 0.1%.

The Examiner admitted that Fabior[®] 0.1% does not teach the claimed concentration of tazarotene, but asserted that:

“the amount of tazarotene in the disclosed composition is a result-effective parameter that will affect the pharmacological and pharmacokinetic properties of the final composition. In this manner, the amount of a specific ingredient in a composition is clearly a result-effective parameter that a person of ordinary skill in the art would routine optimize.”

Office action, p. 3. Applicant respectfully traverses this rejection.

“To reject a claim based on [teaching, suggestion, or motivation] rationale, Office personnel must resolve the *Graham* factual inquiries. Then Office personnel must articulate the following:

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference . . . ;

(2) a finding that there was reasonable expectation of success”

MPEP § 2143 (9th Ed., Rev. 08.2017, Jan. 2018, p. 2100-230) (Emphasis added).

The Examiner appears to assert that the motivation to modify the tazarotene concentration is found in Fabior[®] 0.1% itself because the Examiner asserted that the amount of tazarotene in Fabior[®] 0.1% is a result-oriented parameter that a person of ordinary skill would routinely optimize. Office action, p. 3. The Examiner further states at page 5 of the Office action that “optimization of these parameters is a routine practice, and consequently, would be prima facie obvious, absent factual evidence demonstrating an unexpected benefit of the claimed invention. Such rejection is in clear error, as the Examiner has failed to consider factual evidence submitted in the specification which clearly does demonstrate an unexpected benefit of the claimed invention. Consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. *In re Margolis*, 785 F.2d 1029, 1031, 228 USPQ 940, 941-42 (Fed. Cir. 1986).

More specifically, the Examiner has not articulated any reason why there would be reasonable expectation of success for reducing the tazarotene to less than half the concentration of tazarotene in Fabior[®] 0.1%, as required by the present jurisprudence and the MPEP guidance. *In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006) (A fact finder “must provide some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct. . . . [T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”); *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 418; 127 S.Ct. 1727, 1741 (2007) (“Rejection on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the

legal conclusion of obviousness.”). In particular, the Examiner has not articulated the reason why there would be reasonable expectation of success for achieving better treatment efficacy when the tazarotene concentration is reduced to less than half of the concentration of tazarotene in Fabior® 0.1%. On the other hand, a lack of reasonable expectation of success for the Examiner’s proposed modification of Fabior® 0.1% is evidenced by the fact that the manufacture of Fabior® 0.1% has not produced a commercial tazarotene foam with less than 0.1% tazarotene.

In contradistinction, the present inventors unexpectedly and surprisingly discovered that the presently claimed emulsion composition having 0.045% tazarotene is more efficacious in treating acne than a commercial emulsion having 0.1% tazarotene, at least as measured by Evaluator’s Global Severity Score (“EGSS”) and reduction of inflammatory lesions. *In re Soni*, 34 U.S.P.Q.2d 1684, 1687 (“[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.”). See Tables 6 and 7 of the present specification, as filed, which presents factual evidence which clearly demonstrates an unexpected benefit of the claimed invention. For the Examiner’s convenience, Tables 6 and 7 are reproduced immediately below.

TABLE 6

Treatment % Success (ITT) at 12 Weeks			
	Combined Placebo N = 69	Composition A N = 69	Tazorac® 0.1% Cream N = 72
EGSS - Clear or Almost Clear Inflammatory Lesions	10.1%	18.8%	16.7%
Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions			
Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

TABLE 7

	Treatment % Success (PP)		
	Combined Placebo N = 57	Composition A N = 54	Tazorac ® 0.1% Cream N = 56
EGSS - Clear or Almost Clear	12.3%	20.4%	16.1%
Inflammatory Lesions	-14.2	-18.3	-18.2
Non-inflammatory Lesions	-11.8	-20.8	-21.9

Since a composition having a tazarotene less than half of the concentration of Fabior® 0.1%, as recited in independent claims 1 and 28, is surprisingly more efficacious than a composition having the same concentration as Fabior® 0.1%, the claimed invention is clearly nonobvious over Fabior® 0.1%.

Additionally in response to the Examiner's assertions that the claim limitation "as a sole active pharmaceutical ingredient" (presented in original dependent claim 5, and now incorporated into independent claim 1) does not preclude additional active agents because the claim preamble "comprising" is open ended, such further comments are additionally in clear error. While the use of "comprising" in the preamble may initially signal that the entire claim is presumptively open-ended, any such initial presumption is clearly overcome with respect to the number of active agents permitted in these claims by use of the subsequent expressly stated limitation that tazarotene is a sole active pharmaceutical ingredient in such claims.

Rejection of claims 8-11, 16, 18, and 19 under 35 U.S.C. § 103 as being unpatentable over Fabior® 0.1% in view of Singh

Claims 8-11, 16, 18, and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior® 0.1% in view of Singh. Applicant respectfully traverses this rejection with respect to the present amended claims because the combination of Fabior® 0.1% and Singh does not teach or suggest all of the limitations of each of remaining claim. Moreover, the combination of Fabior® 0.1% and Singh does not provide teaching, suggestion, or motivation to reduce the tazarotene to 0.045% with reasonable expectation of better efficacy than a composition having 0.1% tazarotene as demonstrated in the present application.

As presented above, Fabior[®] 0.1% does not teach or suggest any tazarotene composition having 0.045%. Adding Singh to show disclosure of carbomers still does not show that the combination of Fabior[®] 0.1% and Singh teaches or suggests any tazarotene composition having 0.045%. In other words, the combination of Fabior[®] 0.1% and Singh still does not teach or suggest all of the limitations of each of the rejected and newly added claims. Therefore, all claims are nonobvious over Fabior[®] 0.1% in view of Singh.

Moreover, as presented above, a claimed composition having less than half of the tazarotene concentration of Fabior[®] 0.1% was shown surprisingly to have better efficacy in treating acne than a composition having 0.1% tazarotene. Adding Singh merely to show disclosure of carbomers still does not negate this fact. Since there is nothing in the combination of Fabior[®] 0.1% and Singh that suggests that reducing Fabior[®] 0.1%'s tazarotene concentration would result in better efficacy with any reasonable expectation of success, the present claimed invention is further nonobvious over Fabior[®] 0.1% in view of Singh.

Rejection of claims 7 and 17 under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1% in view of Fiume

Claims 7 and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Fabior[®] 0.1% in view of Fiume. Applicant respectfully traverses this rejection because the combination of Fabior[®] 0.1% and Fiume does not teach or suggest all of the limitations of remaining claim 7. Moreover, the combination of Fabior[®] 0.1% and Fiume does not provide teaching, suggestion, or motivation to reduce the tazarotene to 0.045% with reasonable expectation of better efficacy than a composition having 0.1% tazarotene.

As presented above, Fabior[®] 0.1% does not teach or suggest any tazarotene composition having 0.045%. Adding Fiume merely to show disclosure of diethyl sebacate still does not show that the combination of Fabior[®] 0.1% and Fiume teaches or suggests any tazarotene composition having 0.045%. In other words, the combination of Fabior[®] 0.1% and Fiume still does not teach or suggest all of the limitations of claim 7. Therefore, this claim is nonobvious over Fabior[®] 0.1% in view of Fiume.

Moreover, as presented above, a claimed composition having less than half of the tazarotene concentration of Fabior[®] 0.1% was shown surprisingly to have better efficacy in

treating acne than a composition having 0.1% tazarotene. Adding Fiume to show disclosure of diethyl sebacate still does not negate this fact. Since there is nothing in the combination of Fabior® 0.1% and Fiume that suggests that reducing Fabior® 0.1%'s tazarotene concentration would result in better efficacy with any reasonable expectation of success, the present claimed invention is further nonobvious over Fabior® 0.1% in view of Fiume.

Rejection of claims 1-23 on the ground of nonstatutory double patenting

Claims 1-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of copending Application No. 15/977088. As this is a provisional rejection, and as no claims have yet been indicated as otherwise being allowable, Applicant requests to defer filing of any required Terminal Disclaimer, or cancelling of corresponding claims in one of the applications, until otherwise allowable claims are indicated.

Rejection of claims 1-23 under 35 U.S.C. § 101 over copending Application No. 16/179,561

Claims 1-23 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-23 of copending Application No. 16/179,561. Reconsideration of this provisional rejection is respectfully urged in view of the amendments to the claims in each of such applications.

Conclusion

Since Fabior® 0.1% or its combination with Singh or Fiume does not teach or suggest all of the limitations of each of pending claims 1, 4, 6-12, and 24-28, a *prima facie* case of obviousness of the present claims over Fabior® 0.1%, or its combination with Singh or Fiume, has not been established. Alternatively, since evidence has been presented in the application that the claimed composition having less than half of Fabior® 0.1%'s tazarotene concentration surprisingly had better efficacy than a composition having Fabior® 0.1%'s tazarotene concentration, such evidence of unexpected results clearly overcome any alleged case of *prima facie* obviousness of the claimed invention over Fabior® 0.1% or its combination with Singh or Fiume.

Application Serial Number 16/179,576
Response dated July 19, 2019
Reply to Office Action dated March 20, 2019

In view of the foregoing, it is submitted that the claims are patentable and in condition for allowance. Allowance of the claims at an early date is solicited.

Precautionary Fee-Charge Authorization

By way of precaution, the Commissioner is authorized to charge any underpayment of fees or fee amounts not otherwise authorized but necessary for the consideration of this paper or the continued pendency of this application and to credit any overpayment to Deposit Account Number 03-3875 of Harter Secrest & Emery LLP.

Please grant any extensions of time necessary for the filing of this Amendment.

Respectfully submitted,

/Andrew J. Anderson/

Andrew J. Anderson, Reg. No. 33,564

Attorney for the Applicant
585-231-1157

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. **(currently amended)** A topical pharmaceutical composition for treating a skin disease, comprising:
 a sole active pharmaceutical ingredient consisting of tazarotene or a pharmaceutically acceptable tazarotenic acid salt ~~present in the composition~~ at a ~~positive~~ concentration of ~~in the range from about 0.01 to 0.049~~ 0.045 percent by weight of the composition; and
 a dermatologically acceptable oil-in-water emulsion vehicle; wherein said composition is an oil-in-water emulsion lotion.
2. **(cancelled)**
3. **(cancelled)**
4. **(original)** The topical pharmaceutical composition of claim 1, wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion.
5. **(cancelled)**
6. **(original)** The topical pharmaceutical composition of claim 1, wherein an oil phase of the emulsion comprises a liquid oil component comprising a dicarboxylic acid ester (“DCAE”), a monocarboxylic acid ester (“MCAE”), or combinations thereof.
7. **(original)** The topical pharmaceutical composition of claim 1, wherein an oil phase of the emulsion comprises diethyl sebacate.
8. **(original)** The topical pharmaceutical composition of claim 1, wherein an aqueous phase of the emulsion comprises water and a carbomer homopolymer.

9. **(original)** The topical pharmaceutical composition of claim 1, wherein an aqueous phase comprises water, a carbomer homopolymer, and a polymeric emulsifier; and wherein an oil phase comprises at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil.

10. **(original)** The topical pharmaceutical composition of claim 1, wherein the oil phase comprises diethyl sebacate and mineral oil.

11. **(original)** The topical pharmaceutical composition of claim 1, wherein the oil phase consists of diethyl sebacate and mineral oil.

12. **(original)** The topical pharmaceutical composition of claim 1, having a pH of about 4 to about 6.

13-23 (Cancelled)

24. **(New)** The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
diethyl sebacate;
light mineral oil;
sorbitan monooleate;
sorbitol solution, 70%;
methylparaben;
propylparaben;
edetate disodium dihydrate
carbomer polymer type B;
carbomer homopolymer type A;
sodium hydroxide;
purified water.

25. **(New)** The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
1 - 5 weight % diethyl sebacate;
5 - 15 weight % light mineral oil;
0.01 - 1 weight % sorbitan monooleate;
5 - 15 weight % sorbitol solution, 70%;
0.05 - 0.3 weight % methylparaben;
0.01 - 0.1 weight % propylparaben;
0.02 - 0.1 weight % edetate disodium dihydrate;
0.1 - 1 weight % carbomer polymer type B;
0.2 - 1.5 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 $\pm$ 0.5; and
purified water, q.s. to 100 weight %.

26. **(New)** The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
2 - 4 weight % diethyl sebacate;
5 - 10 weight % light mineral oil;
0.02 - 0.5 weight % sorbitan monooleate;
7 - 12 weight % sorbitol solution, 70%;
0.1 - 0.3 weight % methylparaben;
0.01 - 0.05 weight % propylparaben;
0.02 - 0.7 weight % edetate disodium dihydrate;
0.2 - 0.7 weight % carbomer polymer type B;
0.3 - 1 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 $\pm$ 0.5; and
purified water, q.s. to 100 weight %.

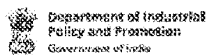
27. **(New)** The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
2.5 – 3.5 weight % diethyl sebacate;
7.5 – 8.5 weight % light mineral oil;
0.05 – 0.2 weight % sorbitan monooleate;
10 - 11 weight % sorbitol solution, 70%;
0.1 - 0.2 weight % methylparaben;
0.02 – 0.04 weight % propylparaben;
0.03 – 0.06 weight % edetate disodium dihydrate;
0.3 – 0.05 weight % carbomer polymer type B;
0.5 – 0.7 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 $\pm$ 0.5; and
purified water, q.s. to 100 weight %.

28. **(New)** A topical pharmaceutical composition consisting essentially of:

0.045 weight % tazarotene;
2.97 weight % diethyl sebacate;
8.03 weight % light mineral oil;
0.1 weight % sorbitan monooleate;
10.7 weight % sorbitol solution, 70%;
0.17 weight % methylparaben;
0.03 weight % propylparaben;
0.05 weight % edetate disodium dihydrate;
0.4 weight % carbomer polymer type B;
0.6 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 $\pm$ 0.5; and
purified water, q.s. to 100 weight %.

Detail	
APPLICATION NUMBER	2461/MUM/2009
APPLICANT NAME	LYKA LABS LIMITED
DATE OF FILING	22/10/2009 16:15:56
E-MAIL	gopanair@gnalpr.net
PRIORITY DATE	NA
TITLE OF INVENTION	"TOPICAL FORMULATION CONTAINING HALOBETASOL PROPIONATE AND TAZAROTENE"
PUBLICATION DATE (U/S 11A)	30/03/2012
Application Status	
Status	Application Published



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Page last updated on: 21/1/2016
 Visitors: 02902

DUPLICATE

FORM 2 THE PATENTS ACT 1970 (39 of 1970) & The Patents Rules, 2003 COMPLETE SPECIFICATION (See section 10 and rule 13)
1. TITLE OF THE INVENTION: "TOPICAL FORMULATION CONTAINING HALOBETASOL PROPIONATE AND TAZAROTENE"
2. APPLICANT: (a) NAME: Lyka Labs Limited. (b) NATIONALITY: Indian Company incorporated under the Indian Companies Act, 1956 (c) ADDRESS: 101, Shivshakti Industrial Estate, Andheri-Kurla Road, Andheri (East), Mumbai 400059, Maharashtra, India.
3. PREAMBLE TO THE DESCRIPTION: The following specification particularly describes the invention and the manner in which it is to be performed:

2404 रूपरेखा नकद/मनी ऑर्डर द्वारा
CBR संख्या. 2278 दि. 21-10-2010

के तहत प्राप्त हुए

लेखक

अन्तिम विनिर्देश के पश्चात संपूर्ण विनिर्देश

12-1 OCT 2010

काइल किया गया।

COMPLETE AFTER PROVISIONAL

COMPLETE SPECIFICATION FILED ON 21 OCT 2010

2461 | मुंबई | 2009
MUM

22 OCT 2009

TECHNICAL FIELD OF INVENTION:

The present invention relates to a topical pharmaceutical composition comprising combination of therapeutically effective amount of high potency corticosteroid such as Halobetasol propionate and retinoid such as Tazarotene, useful for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis. The invention further relates to process for preparation thereof.

BACKGROUND OF THE INVENTION:

Proliferative skin diseases are widespread throughout the world and afflict millions of humans. The expression "proliferative skin diseases" means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases includes psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant kertosis, acne and seborrheic dermatitis in humans.

Among other proliferative skin diseases; psoriasis is a chronic skin disorder that affects 2-4% of the population world-wide.

As psoriasis is a nonfatal disease, its profound impact on the overall quantity of life and well-being is often underestimated. It has a significant effect on the physical, social, psychological and financial avenues of life and an early and aggressive treatment is required to prevent disease progression.

Many patients require life-long treatments for repeated relapses. Treatments for psoriasis have thus far included topicals (including anthralin), steroids, vitamin D, analogues and retinoids, such as tazarotene and other forms of treatment include systemic

21 OCT 2010

immunosuppressant such as methotrexate and cyclosporin, phototherapy such as broad and narrow-band ultraviolet Type B (UVB) and Goeckerman treatment, which is a combination of tar and UVB therapy. Recently a new class of drugs, the biologics, has also been approved for the treatment of psoriasis.

Though monotherapies are effective for the treatment of psoriasis, evidences are accumulating that combining topical retinoid, specifically Tazarotene with other established antipsoriatic therapies result in enhanced efficacy and reduced adverse events. In particular, concomitant use of topical Tazarotene with a mid-potency or high-potency corticosteroid in the treatment of psoriatic plaques enhances efficacy and reduces the risk of corticosteroid skin atrophy. The results of completed Phase III clinical trials of this agent indicate a beneficial effect in moderate to severe plaque psoriasis.

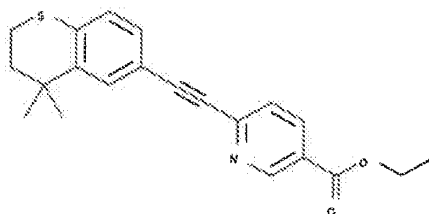
Retinol have been defined narrowly as comprising vitamin A (retinol) and its derivatives, such as vitamin A aldehyde (retinal) and vitamin A acid (retinoic acid), which are metabolites of natural vitamin A. However, subsequent research has resulted in a larger class of chemical compounds that are termed retinoids because they have biological actions similar to the parent vitamin A, even though there may be great structural dissimilarities. Thus, Retinol (Vitamin A) is an organic molecule that is not synthesized in the body; therefore, it must be obtained from the diet, as either preformed retinol or its precursor beta carotene, which is then converted *in vivo* into retinol.

Further, Retinol binds to several retinoic acid receptors in the nucleus, including α , β and γ with receptor γ being the predominant in human epidermis. Tazarotene is a vitamin A derivative that is converted *in vivo* into its active agent, Tazarotene acid, which binds to all three retinoic acid receptors with particularly increased selectivity for receptors β and γ . It has little affinity for the retinoic X receptors.

Tazarotene is mainly used for the treatment of psoriasis, acne vulgaris and sun damaged skin (photodamage). Tazarotene induces the expression of tazarotene-induced gene 3 (TIG3), a tumor suppressor gene. In psoriasis, Tazarotene acid normalizes abnormal keratinocyte differentiation, decreases expression of inflammatory markers and reduces keratinocyte hyperproliferation. Thus, it is very useful as an anti-psoriatic agent.

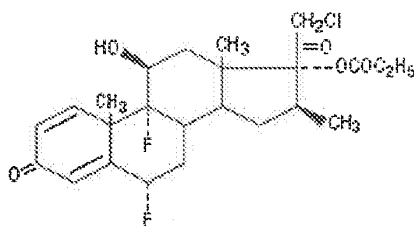
21 OCT 2010

Chemically, Tazarotene is ethyl 6-[2-(4,4-dimethyl-3,4 dihydro 2H 1 benzothiopyran 6-yl)ethynyl]pyridine-3-carboxylate. It has the following structural formula:



Further, like other topical corticosteroids, Halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Chemically, Halobetasol propionate is 21-chloro-6 α , 9 difluoro 11 β , 17 dihydroxy 16 β methylpregna-1, 4 diene-3 20-dione, 17-propionate, C₂₅H₃₁ClF₂O₅. It has the following structural formula:



Moreover, methods for the treatment of inflammatory

dermatoses by administering topical compositions comprising a corticosteroid such as clobetasol propionate, triamcinolone acetonide and hydrocortisone along with a retinoid such as tretinoin in amounts which are effective for treating the dermatoses is disclosed in US5998395.

US2004192662 provides a method for treating proliferative skin diseases comprising the administration of an effective amount of Tazarotene and an effective amount of a corticosteroid (mometasone furoate and fluocinolone acetonide) useful for treating psoriasis.

Indian Patent Application No.1741/MUM/2007 (corresponding PCT Publication no WO2009063491) relates to process for preparation of topical compositions comprising arbutin, corticosteroid (triamcinolone or desonide), retinoid (tretinoin) and optionally a sun protection factor (SPF) for the treatment of skin diseases includes melasma, ephelides, post inflammatory hyperpigmentation, dermal blemishes, non-congenital hyperpigmentation, and solar lentigo.

An article titled "In vitro compatibility of tazarotene with other topical treatments of psoriasis" by Hecker D, Worsley J, Yuch G, Lebwohl M., discloses the compatibility of tazarotene gel with 15 other topical steroids of different potencies, used in the treatment of psoriasis.

An article titled "Tazarotene 0.1% gel plus corticosteroid cream in the treatment of plaque psoriasis" by Lebwohl et al discloses a combination of 0.1% tazarotene gel with either placebo, low potency steroid (0.01% fluocinolone acetonide cream), mid-potency steroid (0.1% mometasone furoate cream) or high-potency steroid (0.05% fluocinonide cream). The said article illustrated that 0.1% Tazarotene gel once-daily in combination with once-daily application of mid- or high-potency topical steroid achieved a significantly greater reduction in scaling, erythema and overall lesion severity than tazarotene once-daily with placebo. Similar studies by Tangchetti et al. and Gollnick et al. confirmed that the use of mid- and high-potency steroids can enhance the efficacy of tazarotene in significantly improving psoriasis.

An article titled "The efficacy of topical tazarotene monotherapy and combination therapies in psoriasis" by John Koo et al discloses tazarotene in combination with 0.05% diflorasone diacetate which gives reduction of 28% in the epidermal thickness. Further, tazarotene significantly reduced epidermal atrophy induced by 0.05% diflorasone diacetate.

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An article titled "Evaluating the potential clinical benefits of switching patients with plaque psoriasis from calcipotriene to tazarotene treatment" by Coynik D compare the effects of 0.1% tazarotene gel combined with a topical corticosteroid to calcipotriene combined with a topical corticosteroid. The authors concluded that switching patients from calcipotriene to tazarotene could increase efficacy and patient satisfaction.

Thus, in light of above; though there are prior arts describing corticosteroids and retinoids in combination, none of them has specifically evaluated the benefits and effect of the combination comprising Halobetasol propionate and Tazarotene simultaneously.

Accordingly, the present invention discloses an effective combination comprising Halobetasol propionate and Tazarotene useful for treating different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis. Though these two drugs have entirely different modes of action and when combined in a single formulation, have synergistic effects which lead to more rapid clearing and are notably effective for types of psoriasis which have not responded to either corticosteroids or retinoids alone.

OBJECT OF THE INVENTION:

The main object of the current invention is to provide the topical composition comprising Halobetasol propionate and Tazarotene, useful for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis and process for preparation thereof.

SUMMARY OF THE INVENTION:

In accordance with the above objective, the present invention discloses topical composition comprising of high potency corticosteroid such as Halobetasol propionate and retinoid such as Tazarotene having synergistic effect against different types of

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psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis.

In further aspect, the present invention provides a process for preparation of said composition.

In yet another aspect, the present invention provides the said combination in different dosage forms such as cream, ointment, gel or lotion.

DETAILED DESCRIPTION OF THE INVENTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The present invention describes a topical composition for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis which comprises of Halobetasol propionate a synthetic corticosteroid and Tazarotene a retinoid in the form of cream, ointment, gel or lotion.

The term "topical" as employed herein relates to the use of the active ingredient incorporated in a suitable pharmaceutical carrier, and applied at the site of the disease for exertion of local action.

More particularly, the present invention provides the topical composition comprising therapeutically effective amount of Halobetasol propionate and Tazarotene along with pharmaceutically acceptable excipients.

In one of the embodiment, the topical cream/ointment formulation comprises Halobetasol propionate (0.025 to 0.05% w/w) and Tazarotene (0.05 to 0.1% w/w) along with the

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pharmaceutical excipients selected from the group comprising of ointment/cream base like waxes, preservatives, antioxidants, buffering agent, chelating agent, penetration enhancer, surfactant, solubilizer, emulsifier and combinations thereof .

According to the embodiment, the topical cream of Halobetasol propionate and Tazarotene, is prepared using excipients selected from the group consisting of Cetostearyl alcohol, Cetomacrogol 1000, Light liquid paraffin, White soft paraffin, Chlorocresol, Butylated hydroxy toluene, Propylene glycol, Hexylene glycol, Disodium EDTA and Citric acid.

According to another embodiment, the ointment of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Butylated hydroxy toluene, Sorbitan sesquioleate, Propylene glycol, Hexylene glycol, White soft paraffin, White bees wax, Cetyl alcohol, Lanolin anhydrous and Liquid paraffin.

According to the invention, the topical composition of Halobetasol propionate and Tazarotene is in the form of cream that can be prepared by melting oil base excipients, emulsifier and optionally antioxidant; followed by dissolving chelating agent in sufficient quantity of purified water; mixing oil phase and water phase under stirring for the emulsion formation at 60-70°C; this is followed by adding preservatives dissolved in solubilizer, penetration enhancer, etc.; followed by cooling and stirring, till stable cream formation takes place. Active ingredient dissolved in Solubilizer can be added before cream formation or while the cream formation is taking place.

According to the invention, the topical composition of Halobetasol propionate and Tazarotene is in the form of ointment that can be prepared by melting ointment base excipients and mixing surfactant to ointment base; adding active ingredient either by dissolving or suspending in solubilizer under constant stirring; cooling and stirring till ointment formation takes place.

In further embodiment, the topical gel/lotion formulation comprises Halobetasol propionate (0.025 to 0.05% w/w) and Tazarotene (0.05 to 0.1% w/w) along with pharmaceutical excipients selected from the group comprising oil base, preservatives,

antioxidants, buffering agent, chelating agent, penetration enhancer, co-solvent, Carbopol, pH adjuster along with vehicle, surfactant, solubilizer, emulsifier and combinations thereof.

Further, the gel of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Carbopol 980, Carbopol 940, Hydroxy Propyl Cellulose, Disodium EDTA, Benzyl Alcohol, Chlorocresol, Butylated Hydroxytoluene, Ascorbic Acid, Sodium Sulphide, Sodium Metabisulphite, Propylene glycol, Citric acid, Sodium Citrate, Triethanolamine, Sodium Hydroxide, Diethanolamine, Purified Water and Isopropyl alcohol.

According to the present invention, the topical composition of Halobetasol and Tazarotene is in the form of gel that can be prepared by soaking carbopol 980 slurry in sufficient quantity of purified water; dissolving chelating agent in sufficient quantity of purified water and adding to carbopol slurry; adding active ingredients and preservative dissolving or dispersing in solubilizer; this is followed by adding Isopropyl alcohol under stirring; checking the pH and adjusting the pH around 4.0 to 6.0 with 20% triethanolamine (TEA) or Diethanolamine or sodium hydroxide solution, till gel formation takes place.

According to another preferred embodiment, the lotion of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Cetyl alcohol, Sodium Lauryl Sulphate, Propylene glycol, Polyethylene Glycol 400, White soft paraffin, Butylated Hydroxytoluene, Methyl paraben, Propyl paraben and Chlorocresol.

Further, the topical composition of Halobetasol and Tazarotene in the form of lotion is prepared by melting emulsifier, oil base and preservatives and optionally antioxidant by heating at 70-80°C; mixing oil phase and water phase under stirring for the emulsion formation at 60-70°C; followed by adding surfactant etc. for the stable lotion formation. Active ingredient dissolved in solubilizer can be added before emulsion formation or while the emulsion formation is taking place.

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Alternately, lotion can be prepared by dissolving Halobetasol in hot Propylene Glycol and dissolving Tazarotene in Propylene glycol in separate beakers. Simultaneously, dissolving Butylated Hydroxy Toluene in PEG 400; and then adding all the solutions into one vessel followed by mixing, till clear solution is obtained and making up the volume with propylene glycol or PEG 400.

The invention is further illustrated by following non-limiting examples of this combination product:

EXAMPLES:

Example 1:

Composition for the Preparation of Cream:

	Ingredients	Concentration % w/w
Active Ingredients	Halobetasol propionate	0.025 - 0.05%
	Tazarotene	0.05 - 0.1%
Emulsifiers	Cetostearyl alcohol	4.2 - 7.8%
	Cetomacrogol 1000	1.05 - 1.95%
Oil Base	Light Liquid Paraffin	2.8 - 5.2%
	White soft Paraffin	2.8 - 5.2%
Penetration enhancers/ solubilizer	Propylene glycol	6.3 - 10.2%
	Hexylene glycol	7 - 13%
Antioxidant	Butylated Hydroxy Toluene	0.01 - 0.025%
Chelating agent	Disodium EDTA	0.007 - 0.013%
Preservative	Chlorocresol	0.07 - 0.13%
Vehicle	Water	q.s

Process for preparing Cream formulation is as follows:

- 1) Melting oil base excipients, emulsifier and optionally antioxidant;
- 2) dissolving chelating agent in sufficient quantity of purified water;
- 3) mixing oil phase and water phase under stirring for the emulsion formation at 60°-70°C;

- 4) dissolving or dispersing active ingredients in solubilizer and adding to bulk of step 3;
- 5) dissolving preservative in Solubilizer and adding it to bulk of step 4 under stirring;
- 6) cooling and stirring of the bulk till cream formation takes place; and
- 7) adjusting the weight with purified water.

Example 2:

Composition for the Preparation of Ointment:

	Ingredients	Concentration % w/w
Active Ingredients	Halobetasol propionate	0.025 - 0.05%
	Tazarotene	0.05 - 0.1%
Solubilizers	Hexylene glycol	7 - 13%
	Propylene glycol	7 - 13%
Ointment base	White Soft Paraffin	54.95 - 90%
	White Beeswax	21 - 39 %
Surfactant	Sorbitan Sesquioleate	0.105 - 0.195%

Process for preparing Ointment formulation is as follows:

- 1) Melting ointment base excipients and mixing surfactant to ointment base;
- 2) adding active ingredients to bulk (melted ointment base) either by dissolving or dispersing in solubilizer under constant stirring; and
- 3) cooling and stirring the bulk till ointment formation takes place.

Example 3:

Composition for the Preparation of Lotion:

	Ingredients	Concentration % w/v
Active Ingredients	Halobetasol propionate	0.025 - 0.05%
	Tazarotene	0.05 - 0.1%
Oil base	White Soft Paraffin	0.525 - 0.975%
Emulsifier	Cetyl Alcohol	1.33 - 2.47%
Solubilizer	Propylene Glycol	5.25 - 9.75%
Antioxidant	Butylated Hydroxy Toluene	0.01 - 0.025%
Preservatives	Methyl Paraben	0.245 - 0.455%

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	Propyl Paraben	0.035 - 0.065%
Surfactant	Sodium Lauryl Sulphate	0.21 - 0.39%
Vehicle	Water	q.s

Process for preparing Lotion formulation is as follows:

- 1) Melting emulsifier, oil base, and preservatives and optionally antioxidant by heating at 70-80°C;
- 2) mixing oil phase and sufficient water phase under stirring for the emulsion formation at 60°-70°C;
- 3) dissolving or dispersing active ingredients in solubilizer;
- 4) adding active drug either before emulsion formation or during emulsion formation;
- 5) dissolving surfactant in sufficient purified water and then adding to bulk;
- 6) cooling and stirring the bulk till lotion formation takes place and then making up the volume.

Alternate composition for the Preparation of Lotion:

	Ingredients	Concentration % w/v
Active Ingredients	Halobetasol propionate	0.025 - 0.05%
	Tazarotene	0.05 - 0.1%
Solubilizer	PEG 400	40.25 - 74.75%
Antioxidant	Butylated Hydroxy Toluene	0.014 - 0.026%
Solubilizer	Propylene Glycol	q.s

Alternate process for preparing Lotion formulation is as follows:

- 1) Dissolving Halobetasol in hot Propylene Glycol;
- 2) In a separate beaker dissolving Tazarotene in Propylene glycol;
- 3) dissolving Butylated hydroxy toluene in PEG 400;
- 4) adding all the solutions into one vessel, mixing well till clear solution is obtained and making up the volume with propylene glycol or PEG 400

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Example 4:

Composition for the Preparation of Gel:

	Ingredients	Concentration % w/w
Active Ingredients	Halobetasol propionate	0.025 - 0.05%
	Tazarotene	0.05 - 0.1%
Gelling agent	Carbopol 980	0.595 - 1.105%
Chelating agent	Disodium EDTA	0.035 - 0.065%
Penetration Enhancer/Solubilizer	Propylene Glycol	21 - 39%
Preservative	Benzyl Alcohol	0.3 - 1.3%
Vehicle	Isopropyl Alcohol	7 - 13%
Vehicle	Water	q.s
pH adjusting agent	TEA 20% solution	q.s

Process for preparing Gel formulation is as follows:

- 1) Preparing carbopol 980 slurry in sufficient quantity of purified water;
- 2) dissolving chelating agent in sufficient quantity of purified water and adding to carbopol slurry of step 1;
- 3) dissolving Halobetasol propionate in solubilizer and adding to bulk of step 2;
- 4) dissolving Tazarotene in Benzyl alcohol and adding to bulk of step 3;
- 5) adding Isopropyl alcohol to the bulk of step 4 under stirring;
- 6) checking the pH and adjusting pH with 20% pH adjusting agent about 4.0 to 6.0 till gel formation takes place;
- 7) adjusting the final weight with purified water and mixing well.

Overages of Halobetasol propionate and Tazarotene can be added for the long term stability purpose.

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STABILITY DATA:

Stability study of the product is carried out as per ICH guideline for 6 months at accelerated condition of 40°C / 75% RH and real time condition of 30°C / 65%RH.

Product is stable.

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We Claim,

1. A topical pharmaceutical composition comprising Halobetasol propionate and Tazarotene in therapeutically effective amounts along with pharmaceutically acceptable excipients; useful for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis.
2. The topical pharmaceutical composition as claimed in claim 1, wherein the Halobetasol propionate is present in an amount of 0.025 to 0.05%.
3. The topical pharmaceutical composition as claimed in claim 1, wherein the Tazaroten is present in an amount of 0.05 to 0.1%.
4. The topical pharmaceutical composition as claimed in claim 1, wherein the composition is in the form of cream, ointment, gel or lotion.
5. The topical pharmaceutical composition as claimed in claim 4, wherein the cream formulation contains pharmaceutically acceptable excipients selected from the group consisting of Cetostearyl alcohol, Cetomacrogol 1000, Light liquid paraffin White soft paraffin, Chlorocresol, Butylated hydroxy toluene, Propylene glycol, Hexylene glycol, Disodium EDTA and Citric acid.
6. The topical pharmaceutical composition as claimed in claim 4, wherein the ointment contains pharmaceutically acceptable excipients selected from the group consisting of Butylated hydroxy toluene, Sorbitan sesquioleate, Propylene glycol, Hexylene glycol, White soft paraffin, White bees wax, Cetyl alcohol, Lanolin anhydrous and Liquid paraffin.
7. The topical pharmaceutical composition as claimed in claim 4, wherein the gel formulation contains pharmaceutically acceptable excipients selected from the group consisting of Carbopol 980, Carbopol 940; Hydroxy propyl cellulose,

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Disodium EDTA, Benzyl Alcohol, Chlorocresol, Butylated Hydroxytoluene, Ascorbic acid, Sodium sulphide, Sodium metabisulphite, Propylene glycol, Citric acid, Sodium citrate, Triethanolamine, Sodium hydroxide, Diethanolamine, Purified water and Isopropyl alcohol.

8. The topical pharmaceutical composition as claimed in claim 4, wherein the lotion contains pharmaceutically acceptable excipients selected from the group consisting of Cetyl alcohol, Sodium lauryl sulphate, Propylene glycol, Polyethylene Glycol 400, White soft paraffin, Butylated Hydroxytoluene, Methyl paraben, Propyl paraben and Chlorocresol.
9. The topical pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the cream formulation is prepared by,
 - a) Melting oil base excipients, emulsifier and optionally antioxidant;
 - b) dissolving chelating agent in sufficient quantity of purified water;
 - c) mixing oil phase and water phase under stirring for the emulsion formation at 60°-70°C;
 - d) dissolving or dispersing active ingredients in solubilizer and adding to bulk of step (c);
 - e) dissolving preservative in Solubilizer and adding it to bulk of step (d) under stirring;
 - f) cooling and stirring of the bulk till cream formation takes place; and
 - g) adjusting the weight with purified water.
10. The topical pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the ointment is prepared by,
 - a) Melting ointment base excipients and mixing surfactant to ointment base;
 - b) adding active ingredients to bulk (melted ointment base) either by dissolving or dispersing in solubilizer under constant stirring; and
 - c) cooling and stirring the bulk till ointment formation takes place.

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11. The topical pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the gel formulation is prepared by,

- a) Preparing carbopol 980 slurry in sufficient quantity of purified water;
- b) dissolving chelating agent in sufficient quantity of purified water and adding to carbopol slurry of step (a);
- c) dissolving Halobetasol propionate in solubilizer and adding to bulk of step (b);
- d) dissolving Tazarotene in Benzyl alcohol and adding to bulk of step (c);
- e) adding IPA to the bulk of step (d) under stirring;
- f) checking the pH and adjusting pH with 20% pH adjusting agent about 4.0 to 6.0 till gel formation takes place;
- g) adjusting the final weight with purified water and mixing well.

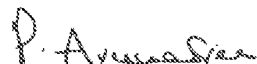
12. The topical pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the lotion is prepared by,

- a) Melting emulsifier, oil base, preservatives and optionally antioxidant by heating at 70-80°C;
- b) mixing oil phase and sufficient water phase under stirring for the emulsion formation at 60°-70°C;
- c) dissolving or dispersing active ingredients in solubilizer;
- d) adding active drug either before emulsion formation or during emulsion formation;
- e) dissolving surfactant in sufficient purified water and then adding to bulk;
- f) cooling and stirring the bulk till lotion formation takes place and then making up the volume.

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13. The topical pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the lotion is alternately prepared by,
- a) Dissolving Halobetasol in hot Propylene glycol;
 - b) In a separate beaker dissolving Tazarotene in Propylene glycol;
 - c) dissolving Butylated hydroxy toluene in PEG 400;
 - d) adding all the solutions into one vessel and mix well till clear solution is obtained and making up the volume with propylene glycol or PEG 400

Dated this 21st day of October, 2010


Dr. P. Aruna Sree
(Regn.No.: IN/PA 998)
Agent for the Applicant

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ABSTRACT:

The invention disclosed herein is a topical pharmaceutical composition comprising combination of Halobetasol propionate and Tazarotene along with pharmaceutically acceptable excipients, useful for the treatment of different types of psoriasis and also discloses the process for preparation thereof.

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TECHNICAL FIELD OF INVENTION:

The present invention relates to topical pharmaceutical composition comprising therapeutic amount of high potency corticosteroid Halobetasol propionate along with retinoid Tazarotene for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis. The said topical pharmaceutical formulation is in the form of cream, ointment, gel or lotion. The invention further relates to process for preparation thereof.

BACKGROUND OF THE INVENTION:

Proliferative skin diseases are widespread throughout the world and afflict millions of humans. The expression "proliferative skin diseases" means benign and malignant *proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation.* Such diseases includes psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant kertosis, acne and seborrheic dermatitis in humans.

Among other proliferative skin diseases; psoriasis is a chronic skin disorder that affects ~2-4% of the population world-wide.

As psoriasis is a nonfatal disease, its profound impact on the overall quantity of life and well-being is often underestimated. It has a significant effect on the physical, social, psychological and financial avenues of life and an early and aggressive treatment is required to prevent disease progression.

There is currently no cure for psoriasis. Many patients require life-long treatments for repeated relapses. Treatments for psoriasis have thus far included topicals (including

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anthralin), steroids, vitamin D, analogues and retinoids, such as tazarotene and other forms of treatment include systemic immunosuppressant such as methotrexate and cyclosporin, phototherapy such as broad and narrow-band ultraviolet Type B (UVB) and Goeckerman treatment, which is a combination of tar and UVB therapy. Recently a new class of drugs, the biologics, has also been approved for the treatment of psoriasis.

Though monotherapies are effective for the treatment of psoriasis, evidences are accumulating that combining topical retinoid, specifically Tazarotene with other established antipsoriatic therapies result in enhanced efficacy and reduced adverse events. In particular, concomitant use of topical Tazarotene with a mid-potency or high-potency corticosteroid in the treatment of psoriatic plaques enhances efficacy and reduces the risk of corticosteroid skin atrophy. The results of completed Phase III clinical trials of this agent indicate a beneficial effect in moderate to severe plaque psoriasis.

Retinol have been defined narrowly as comprising vitamin A (retinol) and its derivatives, such as vitamin A aldehyde (retinal) and vitamin A acid (retinoic acid), which are metabolites of natural vitamin A. However, subsequent research has resulted in a larger class of chemical compounds that are termed retinoids because they have biological actions similar to the parent vitamin A, even though there may be great structural dissimilarities. Thus, Retinol (Vitamin A) is an organic molecule that is not synthesized in the body; therefore, it must be obtained from the diet, as either preformed retinol or its precursor beta carotene, which is then converted *in vivo* into retinol.

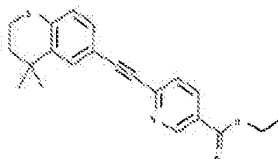
Further, Retinol binds to several retinoic acid receptors in the nucleus, including α , β and γ with receptor γ being the predominant in human epidermis. Tazarotene is a vitamin A derivative that is converted *in vivo* into its active agent, Tazarotene acid, which binds to all three retinoic acid receptors with particularly increased selectivity for receptors β and γ . It has little affinity for the retinoic X receptors.

Tazarotene is mainly used for the treatment of psoriasis, acne vulgaris and sun damaged skin (photodamage). Tazarotene induces the expression of tazarotene-induced gene 3 (TIG3), a tumor suppressor gene. In psoriasis, Tazarotene acid normalizes abnormal

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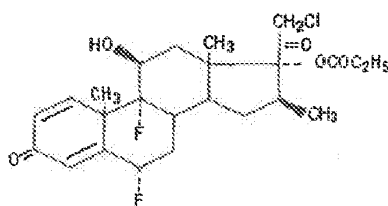
keratinocyte differentiation, decreases expression of inflammatory markers and reduces keratinocyte hyperproliferation. Thus, it is very useful as an anti-psoriatic agent.

Chemically, Tazarotene is ethyl 6-[2-(4,4-dimethyl-3,4-dihydro-2H-1-benzothiopyran-6-yl)ethyl]pyridine-3-carboxylate. It has the following structural formula:



Further, like other topical corticosteroids, Halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Chemically, Halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3-20-dione, 17-propionate, C₂₅H₃₁ClF₂O₅. It has the following structural formula:



Moreover, methods for the treatment of inflammatory dermatoses by administering topical compositions comprising a corticosteroid such as clobetasol propionate, triamcinolone acetonide and hydrocortisone along with a retinoid such as tretinoin in amounts which are effective for treating the dermatoses is disclosed in US5998395.

US2004192662 provides a method for treating proliferative skin diseases comprising the administration of an effective amount of Tazarotene and an effective amount of a corticosteroid (mometasone furoate and fluocinolone acetonide) useful for treating psoriasis.

Indian Patent Application No.1741/MUM/2007 (corresponding PCT Publication no WO2009063491) relates to process for preparation of topical compositions comprising arbutin, corticosteroid (triamcinolone or desonide), retinoid (tretinoin) and optionally a sun protection factor (SPF) for the treatment of skin diseases includes melasma, ephelides, post inflammatory hyperpigmentation, dermal blemishes, non-congenital hyperpigmentation, and solar lentigo.

An article titled "In vitro compatibility of tazarotene with other topical treatments of psoriasis" by Hecker D, Worsley J, Yueh G, Lebwohl M., discloses the compatibility of tazarotene gel with 15 other topical steroids of different potencies, used in the treatment of psoriasis.

Thus in light of above; though there are prior arts describing corticosteroids and retinoids in combination, none of them specifically evaluated the effect of the combination comprising Halobetasol propionate and Tazarotene simultaneously.

Accordingly, the present invention discloses an effective combination comprising Halobetasol propionate and Tazarotene useful for different types treating psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis. Though these two drugs have entirely different modes of action and when combined in a single formulation, have synergistic effects which lead to more rapid clearing and are notably effective for types of psoriasis which have not responded to either corticosteroids or retinoids alone.

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OBJECT OF THE INVENTION:

The main object of the current invention is to provide the topical composition comprising Halobetasol propionate with Tazarotene in the form of cream, ointment, gel and lotion which is useful for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis.

Another object of the present invention is to provide the process for preparation of said topical composition in the form of cream, ointment, gel and lotion.

SUMMARY OF THE INVENTION:

The present invention discloses the topical composition containing high potency corticosteroid Halobetasol propionate along with retinoid Tazarotene in the form of cream, ointment, gel and lotion having synergistic effect against for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis. The invention further relates to the process for preparation thereof.

DETAILED DESCRIPTION OF THE INVENTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The present invention describes topical composition for the treatment of different types of psoriasis such as Plaque Psoriasis, Guttate Psoriasis, Seborrheic Psoriasis, Palmoplantar Psoriasis, Pustular Psoriasis, Palmoplantar Pustulosis or Acropustulosis Erythrodermic Psoriasis, Inverse Psoriasis or Flexural Psoriasis which comprises of Halobetasol

propionate a synthetic corticosteroid with Tazarotene a retinoid in the form of cream, ointment, gel and lotion, useful for the treatment of psoriasis with bacterial infection.

The term "topical" as employed herein relates to the use of the active ingredient incorporated in a suitable pharmaceutical carrier, and applied at the site of the disease for exertion of local action.

In accordance to the above objectives, the present invention provides the topical composition which comprises therapeutically effective amount of Halobetasol propionate with Tazarotene along with pharmaceutically accepted excipients.

In one of the embodiment, the topical cream/ointment formulation comprises Halobetasol propionate (0.05% w/w) and Tazarotene (0.05 to 0.1% w/w) along with the pharmaceutical excipients selected from the group comprising of ointment/cream base like waxes, preservatives, antioxidants, buffering agent, chelating agent, penetration enhancer, surfactant, solubilizer, emulsifier and combinations thereof.

According to the embodiment, the topical cream of Halobetasol propionate and Tazarotene, is prepared using excipients selected from the group consisting of Cetostearyl alcohol, Cetomacrogol 1000, microcrystalline wax, Light liquid paraffin White soft paraffin, Chlorocresol, Butylated Hydroxy Toluene, Propylene glycol, Disodium EDTA and Citric acid.

According to another embodiment, the ointment of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Butylated hydroxy Toluene, Sorbitan Sesquioleate, Propylene glycol, White soft paraffin, White bees wax, Cetyl alcohol, Lanolin anhydrous and Liquid paraffin.

According to the invention, the topical composition of Halobetasol propionate with Tazarotene is in the form of cream that can be prepared by mixing oil phase and water phase under stirring for the emulsion formation at 60-70°C, this is followed by cooling till cream formation takes place followed by adding preservatives, penetration enhancer,

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antifoaming agent etc for the stable cream formation. Active ingredient can be added before cream formation or while the cream formation is taking place.

According to the invention, the topical composition of Halobetasol propionate with Tazarotene is in the form of ointment that can be prepared by melting and mixing the oil base excipients, active ingredient is either dissolved or suspended in oil base and added under constant stirring, followed by adding penetration enhancer, surfactant, antioxidant, etc.

In further embodiment, the topical gel formulation comprises Halobetasol propionate (0.05% w/w) and Tazarotene (0.05 to 0.1% w/w) along with pharmaceutical excipients selected from the group comprising oil base, preservatives, antioxidants, buffering agent, chelating agent, penetration enhancer, co-solvent, Carbopol, pH adjuster along with vehicle, surfactant, solubilizer, emulsifier and combinations thereof.

According to another preferred embodiment, the lotion of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Cetyl alcohol, Sodium Lauryl Sulphate, Propylene glycol, White soft paraffin and Chlorocresol.

According to another preferred embodiment, the gel of Halobetasol propionate and Tazarotene is prepared using excipients selected from the group consisting of Carbopol 980, Carbopol 940; Hydroxy Propyl Cellulose, Disodium EDTA, Chlorocresol, Ascorbic Acid, Sodium Sulphide, Sodium Metabisulphite, Propylene glycol, Citric acid, Sodium Citrate, Triethanolamine, Sodium Hydroxide, Diethanolamine, Purified Water and IPA

According to the invention, the topical composition of Halobetasol with Tazarotene is in the form of lotion that can be prepared by mixing oil phase and water phase under stirring for the emulsion formation at 60-70°C, followed by adding preservatives, penetration enhancer, antifoaming agent etc for the stable lotion formation. Active ingredient can be added before emulsion formation or while the emulsion formation is taking place.

Alternately, lotion can be prepared by dissolving Halobetasol in hot Propylene Glycol and dissolving Tazarotene in Propylene glycol in separate beakers. Simultaneously, dissolving

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Butylated Hydroxy Toluene in PEG 400; and then adding all the solutions into one vessel followed by mixing, till clear solution is obtained.

According to the invention, the topical composition of Halobetasol with Tazarotene is in the form of gel that can be prepared by soaking carbopol in purified water overnight. Active drugs can be dissolved in co-solvent such as Propylene Glycol and added to carbopol gel and mixed properly, then by adjusting pH with triethanolamine (TEA) or Diethanolamine or sodium hydroxide solution. Other inactives can be added to product.

The invention is further illustrated by following non-limiting examples of this combination product:

EXAMPLES:

Example 1:

Composition for the Preparation of Cream:

	Ingredients	Concentration
Active Ingredients	Halobetasol propionate	0.05% w/w
	Tazarotene	0.1 % w/w
Emulsifiers	Cetostearyl alcohol	4.2-7.8 %
	Cetomacrogol 1000	1.05-1.95 %
Oil Base	Light Liquid Paraffin	2.8-5.2 %
	White soft Paraffin	2.8-5.2 %
Penetration enhancers	Propylene glycol	6.3-10.2 %
	Hexylene glycol	7-13 %
Antioxidant	Butylated Hydroxy Toluene	0.01-0.025%
Chelating agent	Disodium EDTA	0.007-0.013 %
Preservative	Chlorocresol	0.07-0.13 %
Vehicle	Water	q.s

Process for preparing cream formulation is as follows:

- 1) Melting oil base excipients, emulsifier and antioxidant;
- 2) Dissolving, chelating agent in sufficient quantity of purified water;

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- 3) Mixing oil phase and water phase under stirring for the emulsion formation at 60°-70°C
- 4) Dissolving or dispersing active ingredients in Solubilizer and adding to bulk of step 3. Adding preservative to bulk of step 4 under stirring;
- 5) Cooling and stirring of the bulk till cream formation takes place; and
- 6) Adjusting the weight with purified water

Example 2:

Composition for the Preparation of Ointment:

	Ingredients	Concentration
Active Ingredients	Halobetasol propionate	0.05% w/w
	Tazarotene	0.05 to 0.1% w/w
Solubilizers	Hexylene glycol	7-13 %
	Propylene glycol	7-13 %
Ointment base	White Soft Paraffin	54.95-90 %
Surfactant	Sorbitan Sesquioleate	0.105-0.195 %
	White Beeswax	21-39 %

Process for preparing ointment formulation is as follows:

- 1) Melting ointment base excipients and mixing surfactant to ointment base;
- 2) Adding active ingredients to bulk (melted ointment base) either by dissolving or dispersing in solubilizer; and
- 3) Cooling and stirring the bulk till ointment formation takes place.

Example 3:

Composition for the Preparation of Lotion:

	Ingredients	Concentration
Active Ingredients	Halobetasol propionate	0.05% w/w
	Tazarotene	0.05 to 0.1% w/w
Oil base	White Soft Paraffin	0.525-0.975 %
Emulsifier	Cetyl Alcohol	1.33-2.47 %
Solubilizer	Propylene Glycol	5.25-9.75 %

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Antioxidant	Butylated Hydroxy Toluene	0.01-0.025%
Preservatives	Methyl Paraben	0.245-0.455 %
	Propyl Paraben	0.035-0.065 %
Surfactant	Sodium Lauryl Sulphate	0.21-0.39 %
Vehicle	Water	q.s

Process for preparing lotion formulation is as follows:

- 1) Melting emulsifier, oil base and preservatives by heating at 70-80°C;
- 2) Mixing oil phase and sufficient water phase under stirring for the emulsion formation at 60°-70°C;
- 3) Dissolving or dispersing active ingredients in Solubilizer;
- 4) Adding active drug either before emulsion formation or during emulsion formation;
- 5) Dissolving surfactant in sufficient purified water and then adding to bulk;
- 6) Cooling and stirring the bulk till lotion formation takes place and then making up the volume.

Alternate composition for the Preparation of Lotion:

	Ingredients	Concentration
Active Ingredients	Halobetasol propionate	0.025-0.05 %
	Tazarotene	0.05-0.1 %
Solubilizer	PEG 400	40.25-74.75 %
Antioxidant	Butylated Hydroxy Toluene	0.014-0.026 %
Solubilizer	Propylene Glycol	q.s

Alternate process for preparing lotion formulation is as follows:

- 1) Dissolve Halobetasol in hot Propylene Glycol.
- 2) In a separate beaker dissolve Tazarotene in Propylene glycol.
- 3) Dissolve Butylated Hydroxy Toluene in PEG 400.
- 4) Add all the solutions into one vessel and mix well till clear

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Example 4:

Composition for the Preparation of Gel:

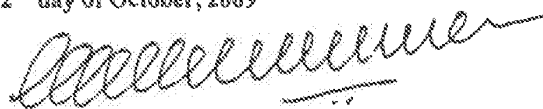
	Ingredients	Concentration
Active Ingredients	Halobetasol propionate	0.05% w/w
	Tazarotene	0.05 % w/w
Gelling agent	Carbopol 980	0.595-1.105 %
Chelating agent	Disodium EDTA	0.035-0.065 %
Penetration Enhancer/Solubilizer	Propylene Glycol	21-39 %
Antioxidant	Butylated Hydroxy Toluene	0.014-0.026 %
	Benzyl Alcohol	0.3-1.3 %
Vehicle	Iso Propyl Alcohol	7-13 %
Vehicle	Water	q.s
pH adjusting agent	TEA 20% solution	q.s

Process for preparing gel formulation is as follows:

- 1) Preparing carbopol 980 slurry in sufficient quantity of purified water.
- 2) Dissolving chelating agent and buffering agent in sufficient quantity of purified water and adding to carbopol slurry of step 1
- 3) Dissolving or dispersing active ingredients and preservative in Solubilizer and adding to bulk of step 2
- 4) Adding IPA to the bulk of step 3 under stirring
- 5) Checking the pH and adjusting pH with 20% pH adjusting agent about 4.0 to 6.0 till gel formation takes place.
- 6) Adjusting the final weight with purified water and mixing well.

●Grages of Halobetasol propionate and Tazarotene can be added for the long term stability purpose.

Dated this the 22nd day of October, 2009



Dr. Gopakumar G. Nair
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L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2016 ACS on STN

ACCESSION NUMBER: 2012:481417 CAPLUS Full-text

DOCUMENT NUMBER: 157:209393

TITLE: Topical formulations containing halobetasol
propionate and tazarotene

INVENTOR(S): Gandhi, Narendra Ishwarlal; Samant, Rajan Shantaram

PATENT ASSIGNEE(S): Lyka Labs Limited, India

SOURCE: Indian Pat. Appl., 33pp.

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DOCUMENT TYPE: Patent

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PATENT INFORMATION:

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AB The invention disclosed herein is a topical pharmaceutical composition comprising combination of halobetasol propionate and tazarotene along with pharmaceutically acceptable excipients, useful for the treatment of different types of psoriasis and also discloses the process for preparation thereof. Thus, an ointment contained halobetasol propionate 0.025-0.05, tazarotene 0.05-0.1, hexylene glycol 7-13, propylene glycol 7-13, white soft paraffin 54.95-90, white beeswax 21-39, and sorbitan sesquioleate 0.105-0.195%.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/179,576	11/02/2018	Angel Arturo	99336.000342

CONFIRMATION NO. 1093

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HSE/Valeant
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Title: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

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NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000207-CIP	1093
134756	7590	03/20/2019	EXAMINER	
HSE/Valeant			CRUZ, KATHRIEN ANN	
1600 Bausch & Lomb Place			ART UNIT	PAPER NUMBER
Rochester, NY 14604			1621	
			NOTIFICATION DATE	DELIVERY MODE
			03/20/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patent@hselaw.com

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-23 is pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 12-15, 20-23 are rejected under 35 U.S.C. 103 as being unpatentable over Fabior® (Tazarotene) Foam 0.1% [package insert]. Research Triangle Park, NC: Stiefel Laboratories, Inc; 2012 (Fabior).

Fabior Foam contains tazarotene, 1 mg/g in aqueous-based white to off-white foam vehicle consisting of butylated hydroxytoluene, cetearoth-12, citric acid anhydrous, diisopropyl adipate, light mineral oil, potassium citrate monohydrate, potassium sorbate, purified water, and sorbic acid.

The difference between Fabior and the claimed formulaton is that Fabior does not teach the invention with particularity so as to amount to anticipation (See M.P.E.P. §

2131: "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).). However, based on the above, Fabior teaches the elements of the claimed invention with sufficient guidance, particularity, and with a reasonable expectation of success, that the invention would be *prima facie* obvious to one of ordinary skill (the prior art reference teaches or suggests all the claim limitations with a reasonable expectation of success. See M.P.E.P. § 2143).

Fabior may not teach the recited effective amounts of tazarotene. However, the amount of tazarotene in the disclosed composition is a result-effective parameter that will affect the pharmacological and pharmacokinetic properties of the final composition. In this manner, the amount of a specific ingredient in a composition is clearly a result-effective parameter that a person of ordinary skill in the art would routinely optimize.

Specifically, it would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve a desired results. For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

Therapeutic efficacy and toxicity, e.g., ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population), can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50} . Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration. The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active ingredient or to maintain the desired effect. Factors which can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered once or twice daily every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts can vary from micrograms to 100,000 micrograms, up to a maximum total dose, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.

In this way, optimization of these parameters is a routine practice, and consequently, would be prima facie obvious, absent factual evidence demonstrating an unexpected benefit of the claimed amount(s).

With regards to the claim limitation of "as a sole active pharmaceutical ingredient" (claim 23), the claims recite "comprising" and "contains" which is open ended claim language which does not precluded additional active agents. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPO 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPO 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPO 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). In *Gillette Co. v. Energizer Holdings Inc.*, 405 F.3d 1367, 1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses

razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open-ended. "The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." *Id.* In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" that is by its nature closed. *Id.* The court also emphasized that reference to "first," "second," and "third" blades in the claim was not used to show a serial or numerical limitation but instead was used to distinguish or identify the various members of the group. *Id.*

Claims 8-11,16, 18 and 19 are rejected under 35 U.S.C. 103 as being unpatentable over Fabior in view of Singh et al., Dosage Forms: Non-Parenteral in Encyclopedia of Pharmaceutical Technology, 2002, Marcel Dekker (Singh))

Fabior may fail to explicitly teach those formulations comprising which are lotions and creams, or those comprising carbomers (thickening agents), as covered by the rejected claims. However, it is for that proposition that the examiner joins Singh, which teaches these formulations with the recited carbomers (polycarylates):

SEMISOLID DOSAGE FORMS

Ointments, creams, and pastes are semisolid dosage forms intended for topical application. They may be applied to the skin, used nasally, rectally, and vaginally. Most of them contain some form of medicament. Medicated ointments are semi-solid preparations intended for application to skin or mucous membranes. Nonmedicated ointments are used as protectants, lubricants, and emollients. Ointment bases used for ointment preparation are of four types, hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases. Hydrocarbon bases have emollient properties and are effective as occlusive dressings (e.g., Petrolatum, USP). Absorption bases permit the incorporation of aqueous solutions to form w/o emulsions (e.g., hydrophilic petrolatum and lanolin). Water-removable bases are also o/w emulsions and are water washable (e.g., hydrophilic ointment). Water-soluble bases have no oleaginous component and are referred to as *greaseless* water-washable bases (e.g., polyethylene glycol ointment). The potential for absorption depends on the choice of the bases, and intended use of the medicament. Appropriate selection of ointment bases is important for dermal therapy. Ointments for rectal preparation (e.g., Tranolane[®] ointment for hemorrhoidal analgesia) and vaginal preparations (e.g., Mycelex-7[®] ointment as antifungal) are available in the market. Creams are semisolid emulsions with one or more medicinal agents intended for external use. The so called *vanishing creams* are o/w emulsions with stearic acid and cold creams are w/o emulsions with an oily base. Creams spread more easily than ointments and are preferred by

some patients. Gels are semisolid systems with dispersions of small or large molecules in an aqueous vehicle with a gelling agent e.g., high molecular weight Carbopols[®] that are cross-linked polyacrylic acid. Some

In this way, those of ordinary skill could have applied the recited formulations to tazarotene in a predictable fashion for the purposes of obtaining a topical drug product. Specifically, Fabior teaches that tazarotene is a drug for acne. Singh is added for the proposition that creams, lotions and gels comprising additives such as carbomers (i.e., polyacrylates) are applicable to topical skin formulations. Since Singh teaches that the particular known technique of using the recited formulations for skin was recognized as part of the ordinary capabilities of one skilled in the art, those of ordinary skill would have recognized that applying the known technique to tazarotene would have yielded

predictable results. Accordingly, formulating tazarotene in the recited formulations, such as creams, lotions and gels, would have been prima facie obvious.

Claims 7 and 17 are are rejected under 35 U.S.C. 103 as being unpatentable over Fabior in view of Fiume et al., Int J Toxicol. 2012 Jul-Aug;31(4 Suppl):5S-76S (Fiume).

The rejected claims cover using diethyl sebacate (DS) instead of diisopropyl adipate. However, substitution of one emollient, or penetration enhancer for another is well within the purview of ordinary skill, see MPEP 2144.06.

Nonetheless, DS is a known and well-characterized emollient and commonly used, See Fiume:

Diethyl Sebacate
110-40-7

Diethyl Sebacate is the
diester of ethyl alcohol
and Sebacic Acid

Fragrance Ingredients;
Plasticizers; Skin-
Conditioning Agents -
Emollient; Solvents



See page 10S, for example.

Therefore, those of ordinary skill could have used DS in the formulation of Fabior as an emollient and penetration enhancer, with a reasonable expectation of success, and in this manner, using DS in a topical formulation would have been prima facie obvious, in the absence of any unexpected benefit.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may

be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-23 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of copending Application No. 15/977088 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '088 application recite a composition (tazarotene) for the treatment of acne. This difference is that the '088 recite "wherein the composition is an oil-in-water emulsion" and the instant application is a lotion as well as the concentration of tazarotene. Taken that both applications disclose the same compound (tazarotene) to treat acne, one of ordinary skills in the art would recognize that both application possess significant overlapping scopes of invention with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S.

186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-23 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-23 of copending Application No. 16/179,561 (reference application). This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

Conclusion

Claims 1-23 is rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN ANN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Monday to Friday from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Melenie Gordon can be reached at telephone number (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1621

<i>Notice of References Cited</i>	Application/Control No. 16/179,576	Applicant(s)/Patent Under Reexamination Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1621	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Fabior® (Tazarotene) Foam 0.1% [package insert]. Research Triangle Park, NC: Stiefel Laboratories, Inc; 2012 (Year: 2012)
	V	Singh et al., Dosage Forms: Non-Parenteral in Encyclopedia of Pharmaceutical Technology, 2002, Marcel Dekker (Year: 2002)
	W	Fiume et al., Int J Toxicol. 2012 Jul-Aug;31(4 Suppl):5S-76S
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20190315

<i>Search Notes</i> 	Application/Control No. 16/179,576	Applicant(s)/Patent Under Reexamination Arturo et al.
	Examiner KATHRIEN A CRUZ	Art Unit 1621

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	03/15/2019	KC

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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EAST Search History**EAST Search History (Prior Art)**

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	61	((("ARTURO") near3 ("Angel"))) OR ((("PILLAI") near3 ("Radhakrishnan"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:09
L2	1	((("ARTURO") near3 ("Angel"))) and ((("PILLAI") near3 ("Radhakrishnan"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:10
L3	9070	tazarotene	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:11
L4	3253	l3 and acne	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:11
L5	2707	l4 and @py<"2017"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:12
L6	556	l5 and "acne vulgaris"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/03/15 16:12

3/ 15/ 2019 4:31:18 PM

C:\Users\kcruz\Documents\EAST\Workspaces\16179561.wsp

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/179,576			
APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760		
TOTAL CLAIMS (37 CFR 1.16(i))	23	minus 20 = *	3			x 100 =	300		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	minus 3 = *				x 460 =	0.00		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL		TOTAL	2020		
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus **	=			x	=	
	Independent (37 CFR 1.16(h))	*	Minus ***	=			x	=	
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus **	=			x	=	
	Independent (37 CFR 1.16(h))	*	Minus ***	=			x	=	
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/179,576	11/02/2018	1629	2180	99336.000207-CIP	23	2

CONFIRMATION NO. 1093

UPDATED FILING RECEIPT



134756
HSE/Valeant
1600 Bausch & Lomb Place
Rochester, NY 14604

Date Mailed: 01/31/2019

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Angel Arturo, Santa Rosa, CA;
Radhakrishnan Pillai, Santa Rosa, CA;

Applicant(s)

Valeant Pharmaceuticals North America, Bridgewater, NJ;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CIP of 15/977,088 05/11/2018
and is a CIP of 15/173,961 06/06/2016
and said 15/977,088 05/11/2018
claims benefit of 62/505,421 05/12/2017
and said 15/173,961 06/06/2016
claims benefit of 62/181,481 06/18/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/26/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/179,576**

Projected Publication Date: 05/09/2019

Non-Publication Request: No

Early Publication Request: No
Title

TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

page 2 of 4

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/179,576	11/02/2018	Angel Arturo	99336.000207-CIP

CONFIRMATION NO. 1093

134756
HSE/Valeant
1600 Bausch & Lomb Place
Rochester, NY 14604

INFORMAL NOTICE



Date Mailed: 01/31/2019

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Angel Arturo
Radhakrishnan Pillai

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/dgela/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Arturo, Angel
Applicant: Valeant Pharmaceuticals North America
Application No.: 16/179,576
Filed: November 2, 2018
Examiner: tbd
Group/Art Unit: tbd
Atty. Docket No.: 99336.000342
Title: TOPICAL COMPOSITIONS AND METHODS FOR TREATING
SKIN DISEASES

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

January 28, 2019

Response to the Notice to File Corrected Application Papers
and
Preliminary Amendment

Dear Sir:

This Response is to the Notice to File Corrected Application Papers dated November 28, 2018; the Applicant hereby amends the above-referenced application as follows:

Amendments to the Specification: begin at page 2 of this paper.

Amendments to the Claims: none.

Amendments to the Drawings: none.

Remarks/Arguments: begin at page 3 of this paper.

Appendix: Substitute Specification (marked-up); Substitute Specification (clean copy).

Application No. 16/179,576
Amendment dated January 28, 2019
Response to Notice to File Corrected Application Papers dated November 28 2018

Amendments to the Specification

Please replace the original Specification with the attached Substitute Specification in accordance with 37 CFR 1.125, which has been formatted as provided by 37 CFR 1.77(b). No new matter has been as added to the Substitute Specification.

ATTACHMENTS:

1. A Substitute Specification (excluding the claims) with markings showing all the changes relative to the immediate prior version of the specification of record.
2. A clean version (without markings) of the same Substitute Specification.

Application No. 16/179,576
Amendment dated January 28, 2019
Response to Notice to File Corrected Application Papers dated November 28 2018

REMARKS/ARGUMENTS

In response to the Notice to File Corrected Application Papers dated November 28, 2018, the present application has been carefully reviewed and amended.

A Substitute Specification is submitted wherein original paragraphs [0022], [0023], and [0063] have been amended consistent with the originally submitted drawings. No new matter has been as added to the Substitute Specification. Entry of the present amendment is accordingly respectfully requested in response to the Notice to File Corrected Application Papers.

CONCLUSION

Should the Examiner consider that additional amendments are necessary to place this application in condition for allowance, the favor is requested of a telephone call to the undersigned for the purposes of discussing such amendments.

Precautionary Fee-Charge Authorization

By way of precaution, the Commissioner is authorized to charge any underpayment of fees or fee amounts not otherwise authorized but necessary for the consideration of this paper or the continued pendency of this application and to credit any overpayment to Deposit Account Number 03-3875 of Harter Secrest & Emery LLP.

Please grant any extensions of time necessary for the filing of this Amendment.

Respectfully submitted,

/Andrew J. Anderson/

Andrew J. Anderson, Reg. No. 33,564
Customer Number 23387
HARTER SECREST & EMERY LLP
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TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of U.S. Patent Application No. 15/173,961, filed June 6, 2016, which claims priority to U.S. Provisional Patent 62/181,481, filed June 18, 2015; and this application is a continuation-in-part application of U.S. Patent Application No. 15/977,088, filed May 11, 2018, which claims priority to U.S. Provisional Patent 62/505,421, filed May 12, 2017.

[0002]

BACKGROUND

[0003] The present invention relates to topical compositions and methods for treating skin diseases such as acne and psoriasis. In particular, this invention relates to topical pharmaceutical compositions comprising tazarotene or a pharmaceutically acceptable tazarotenic acid salt, in an oil-in-water emulsion vehicle, for treating skin diseases.

[0004] The retinoid tazarotene has been commercially available and has been used to treat acne and psoriasis topically. However, tazarotene may cause significant local skin irritation, especially early in the first through fourth weeks of therapy, thus limiting its use for a prolonged period because many patients stop treatment due to skin irritation. The need exists for more effective and safer topical

medicaments with reduced adverse effects for the management of acne, psoriasis and other skin diseases.

SUMMARY OF THE INVENTION

[0005] In general, the present invention provides topical compositions and methods for treating skin diseases such as acne and psoriasis.

[0006] In one aspect, this invention provides a topical pharmaceutical composition for treating skin diseases, including acne and psoriasis, comprising: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0007] In another aspect, this invention provides a method of treating skin diseases, including acne and psoriasis, comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from the skin disease, wherein the composition comprises: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0008] According to other aspects, the topical pharmaceutical composition may comprise tazarotene or the salt thereof at 0.01 to 0.049 percent by weight of the composition, or at about 0.045 percent by weight of the composition.

[0009] According to another aspect, the tazarotene or tazarotenic acid salt may be dissolved in a liquid oil component of the emulsion.

[0010] According to another aspect, the topical pharmaceutical composition may contain the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.

[0011] According to various aspects, the oil phase of the emulsion may comprise a liquid oil component comprising a DCAE, a MCAE, or combinations thereof. In other aspects, the oil phase includes diethyl sebacate as the DCAE.

[0012] According to other aspects, the aqueous phase of the emulsion may comprise water and a carbomer homopolymer.

[0013] According to another aspect, the topical pharmaceutical composition may comprise: an aqueous phase comprising water, a carbomer homopolymer, and a polymeric emulsifier; an oil phase comprising at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil, and the tazarotene or the tazarotenic acid salt. According to other aspects, the aqueous phase may further comprise a humectant or a preservative, such as at least one member selected from the group consisting of methylparaben, propylparaben and sorbitol.

[0014] According to other aspects, the topical pharmaceutical composition may have the form of a lotion, or of a cream.

[0015] According to another aspect, the topical pharmaceutical composition may have a pH of about 4 to about 6.

[0016] For the methods of this invention, the step of applying may be carried out once per day for at least eight weeks. According to one aspect, the applying is carried out once per day for at least twelve weeks.

[0017] According to other aspects, the composition may be applied is to an affected area of a body of a subject suffering from acne vulgaris in order to treat that condition.

[0018] Other features and advantages of the present invention will become apparent from the accompanying drawings and the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

[0019] Figure 1 is a graph of EGSS by visit.

[0020] Figure 2 is a graph of change in inflammatory lesions from baseline.

[0021] Figure 3 is a graph of change in non-inflammatory lesions from baseline.

[0022] Figures 4A, 4B, and 4C are graphs of cutaneous tolerability to burning, stinging, and itching, respectively.

[0023] Figures 5A, 5B, 5C, and 5D ~~are includes~~ graphs of cutaneous safety assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentation, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0024] In general, the present invention provides topical compositions and methods for treating skin diseases, including acne and psoriasis.

[0025] Throughout this disclosure, unless otherwise indicated, the concentration of an ingredient of the composition is in percent by weight of the total composition.

[0026] In one aspect, the topical pharmaceutical composition comprises tazarotene, or a pharmaceutically acceptable salt of tazarotenic acid, at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or the tazarotenic acid salt is included in a composition at a positive concentration less than 0.05 wt%.

[0027] In certain embodiments of the present invention, tazarotene or the tazarotenic acid salt is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition ("wt%"). For example, this component is present in the range from about 0.01 to about 0.049 wt%, or from about 0.01 to about 0.045 wt%, or from about 0.02 to about 0.045 wt%, or from about 0.03 to about 0.045 wt%, or at about 0.045 wt%. Specific concentrations of this component may be 0.01 wt%, 0.015 wt%, 0.02 wt%, 0.025 wt%, 0.03 wt%, 0.035 wt%, 0.04 wt%, and 0.045 wt%.

[0028] In one aspect, the topical pharmaceutical composition comprises an oil-in-water emulsion as a carrier vehicle, in which an internal oil phase is dispersed in a continuous aqueous phase. The emulsion may be a macroemulsion, a

microemulsion, or a nanoemulsion. The composition may have the dosage form of gel, lotion, or cream, or ointment, or liquid, or oil, or spray or foam.

[0029] In addition to the tazarotene active ingredient, the composition of the present invention may comprise one or more dermatologically acceptable excipients, such as liquid oils, waxes viscosity-modifying agents, thickening agents, gelling agents, alcohols, surfactants, chelating agents, buffers, preservatives, humectants, emollients, stabilizers, diluents, dispersing agents, emulsifiers, wetting agents, stabilizers, pH adjusters, solvents or cosolvents.

[0030] The composition of the invention may desirably contain a thickening agent to provide viscosity so that the formulation may be provided in the form of a gel, lotion, cream, or ointment. The thickening agent may be miscible or soluble in an aqueous fluid. Non-limiting examples of suitable thickening agents include acacia, alginic acid and its salts, hyaluronic acid and its salts, carbomers (also known as carboxy vinyl polymers, which are cross-linked polyacrylic acid), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohol, tragacanth, xanthan gum, magnesium aluminum silicate, and bentonite. The thickening agent may also reside in the oil or lipophilic portion of the formulation. Examples of suitable lipophilic thickening agents include cetyl alcohol, stearyl alcohol, glyceryl stearate, white beeswax, microcrystalline wax, hydrogenated polyisobutane polymers, and emulsifying wax.

[0031] A suitable group of thickening agents is carbomers, such as Carbopol® and polycarbophil (The Lubrizol Corporation, Wickliffe, Ohio). Carbopol® homopolymers are polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol. Carbopol® copolymers are polymers of acrylic acid and C₁₀-C₃₀ alkyl acrylate crosslinked with allylpentaerythritol. Carbopol® interpolymers are carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester. Noveon® polycarbophil is a polymer of acrylic acid crosslinked with divinyl glycol.

[0032] A surfactant or emulsifier is optionally included, if desired or required. Pharmaceutically acceptable anionic, cationic, or non-ionic surfactants may be included in a composition of the present invention. Non-ionic surfactants are preferred. Non-limiting examples of non-ionic surfactants are Octoxynol (also known as Macrogol tetramethylbutylphenyl ether, octylphenoxy polyethoxyethanol, or polyoxyethylene octylphenyl ether), such as Octoxynol 1, 3, 5, 8, 9, 10, 12, 13, 16, 30, 40, 70 (wherein the number indicates the number of repeating oxyethylene units), or other Octoxynols that comprise different numbers of repeating units of oxyethylene in the side chain, sorbitan esters (such as sorbitan monooleate and sorbitan monostearate, commonly known by their trade names Span 80 and Span 60), polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade

names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc.), other nonionic surfactants such as Brij® (polyoxyethylene alkyl ether having a formula of $\text{CH}_3-(\text{CH}_2)_{10-18}-(\text{O}-\text{C}_2\text{H}_4)_{1-25}-\text{OH}$), Myrj® (stearic acid esterified with polyoxyethylene having 40-100 repeating oxyethylene units), and long chain fatty alcohols (e.g., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosahexaenoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms).

[0033] In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used. These are polymers of acrylic acid, modified by long chain (C₁₀-C₃₀) alkyl acrylates, and crosslinked with allylpentaerythritol.

[0034] An anionic emulsifier may be used, such as sodium or potassium oleate, triethanolamine stearate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Still other emulsifiers include glyceryl monostearate, polyoxyethylene monooleate, polyoxyethylene monostearate, polyoxyethylene monolaurate, potassium oleate, sodium lauryl sulfate, sodium oleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, triethanolamine oleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene

sorbitan monostearate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monooleate, and polyoxyethylene sorbitan trioleate.

[0035] The formulation desirably contains a dermatologically acceptable humectant such as glycerin, sorbitol, hexylene glycol, propylene glycol, or urea. In addition, the formulation may contain an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. Chelating agents such as EDTA and citric acid and their salts may be included in a formulation of the present invention.

[0036] The liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature. For example, in one embodiment, the liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature of 22 °C. The liquid oil component may be selected from one or more ingredients from the group consisting of dicarboxylic acid esters ("DCAE"), monocarboxylic acid esters ("MCAE"), fish-liver oil, long-chain triglycerides (wherein each side chain has 14-18 carbons, such as peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, olive oil, cotton seed oil, or derivatives thereof), propylene glycol diesters, medium-chain triglycerides (such as those wherein each side chains has 8-10 carbons; e.g., capric/caprylic acid triglycerides), hydrocarbons like mineral oil, light mineral oil, squalene, and squalane, fatty alcohols (such as octyldodecanol and isostearyl alcohol), and fatty acids (such as isostearic acid and oleic acid).

[0037] In some embodiments, the liquid oil component comprises a dicarboxylic acid ester and light mineral oil. In some other embodiments, the liquid oil component comprises one or more long-chain triglycerides.

[0038] The formulation may include other lipophilic liquids in an amount that is sufficient to be miscible with the dicarboxylic acid ester and/or monocarboxylic acid ester. The lipophilic liquid may be an emollient such as lanolin oil, mineral oil, light mineral oil, isostearic acid, squalene, octyldodecanol, fractionated coconut oil, cyclomethicone, or dimethicone.

[0039] In addition to the liquid oil component, the formulation may contain water insoluble or practically insoluble ingredients that are not liquid at room temperature, but are soluble in the liquid oil component.

[0040] A DCAE that is suitable for the present invention has the formula $R_1OOC-(CH_2)_n-COOR_2$, wherein R_1 and R_2 are alkyl groups containing between 1 and 4 carbons or aryl groups and may be the same or may be different and wherein $(CH_2)_n$ is a straight or branched chain and n is between 1 and 12. Examples of DCAEs containing one or more aryl groups are dibenzyl esters of dicarboxylic acids. A preferred dicarboxylic acid ester is diethyl sebacate, which has the formula $CH_3CH_2OOC-(CH_2)_8-COOCH_2CH_3$. Examples of other suitable dicarboxylic acid esters (where R_1 and R_2 are the same) are dimethyl, diethyl, dipropyl, diisopropyl, dibutyl and diisobutyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, and azalate. Examples of suitable dicarboxylic acid esters (where R_1 is different from R_2) are methyl ethyl, methyl propyl, methyl butyl, methyl

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isopropyl, ethyl propyl, ethyl butyl, ethyl isopropyl, and propyl butyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, azalate, and sebacate.

[0041] In some aspects, diethyl sebacate is included at 0.1 to 20 wt%, or at 0.5 to 10 wt%, or at 2 to 4 wt% of the weight of the composition.

[0042] Alternatively, or in combination with the DCAE, the formulation may contain a MCAE. The MCAE that is suitable for the present invention has the formula $\text{CH}_3-(\text{CH}_2)_n-\text{COOR}_1$, wherein R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and wherein $(\text{CH}_2)_n$ is straight or branched chain and n is between 1 and 12. Examples of such monocarboxylic acid esters include methyl, ethyl, propyl, isopropyl, butyl, or an aryl such as benzyl formate, acetate, propionate, butyrate, valerate, laurate, myristate, palmitate, and stearate. Examples of preferred monocarboxylic acid esters are isopropyl palmitate and isopropyl myristate.

[0043] The liquid oil phase may beneficially be used to dissolve one or more of the active ingredients within the emulsion. In one embodiment the tazarotene component is dissolved in the liquid oil phase within the formulation at room temperature. In another embodiment the tazarotene component is suspended within the formulation at room temperature. In the case wherein the tazarotene component is suspended in the formulation, this suspended active ingredient may be micronized, namely that the mean particle size is preferably about 25 microns in diameter or less.

[0044] In one aspect, a composition of the present invention comprises the ingredients at the concentrations shown in Table 1.

Table 1

Compositions of the Present Invention for Treating Skin Diseases

Ingredient	Concentration (wt%)		
	Range 1	Range 2	Range 3
Tazarotene or Tazarotenic Acid Compound	0.01-0.049	0.02-0.045	0.03-0.045
Emollient, Solvent, and/or Thickener	0.5-40	1-25	2-20
Emulsifier	0.25-10	0.5-7	1-5
Humectant	0-15	2-12	3-10
Polymeric Thickener	0.05-2	0.1-1.5	0.3-1
Pharmaceutical Aids	q.s.	q.s.	q.s.
Purified water	q.s. to 100	q.s. to 100	q.s. to 100

[0045] Non-limiting examples of compositions of the present invention are shown in Table 2.

Table 2

Some Emulsion Compositions of the Present Invention for Treating Acne

Ingredient	Function	Concentration (wt%)			
		Range 1	Range 2	Range 3	Composition A
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Note: ⁽¹⁾ These ingredients are broadly classified as Pharmaceutical Aids.

[0046] A lotion having a composition as shown Composition A of Table 2 may be prepared as follows.

[0047] A separate aqueous phase is made. In a manufacturing vessel equipped with a mixing implement (such as a propeller) and temperature control, purified

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water and disodium edetate dihydrate are combined and the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and heated to approximately 75 °C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40 °C with continued mixing. With continuous mixing, Carbopol® 981 and Pemulen™ TR-1 carbomers are added to the mixture and dispersed. Mixing continues until the two carbomers are fully dispersed and hydrated.

[0048] A separate oil phase is made. In a vessel equipped with a mixing implement such as a propeller, diethyl sebacate, and tazarotene are combined. The mixture is agitated until a solution is achieved. With continuous mixing, light mineral oil and sorbitan monooleate are added. Mixing is continued until a solution is obtained.

[0049] In a separate vessel, an approximate 2.5 N solution of sodium hydroxide is prepared.

[0050] With high speed mixing, the oil phase containing the active ingredient (tazarotene) is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Mixing speed is decreased and mixing continued for an additional time of 10 minutes to 1 hour. With continuous mixing, an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5 ± 0.5 . Mixing continues further until a homogeneous lotion is obtained, such as for 30 minutes to 3 hours.

[0051] A first clinical study in acne patients was conducted to compare the efficacy of a composition of the present invention containing tazarotene (the “Composition A” lotion of Table 2).

[0052] A first placebo (“Lotion Placebo”) corresponded to and had a similar viscosity as Composition A but lacked tazarotene. A second placebo (“Cream Placebo”) corresponded to the Lotion Placebo but employed carbomer homopolymer type C in place of carbomer homopolymer type A to yield a higher viscosity emulsion with a viscosity similar to 0.1% tazarotene cream employed in the study. This allows for better blinding of the test formulations and control of the clinical study. In the following results, data for Lotion Placebo and Cream Placebo may be combined and reported as “Combined Placebo”.

[0053] Additionally, commercially available 0.1% tazarotene cream (Tazorac® 0.1% cream) was employed in this clinical study for comparison purposes.

[0054] A double blind, multi-site, randomized clinical study was conducted on patients suffering from acne vulgaris, whereby neither the acne patient nor the investigator knew the identity of the test composition assigned. 210 patients were randomized to receive either Composition A lotion, Tazorac® 0.1% cream, Placebo Lotion and Placebo Cream at a 2:2:1:1 randomization:

69 subjects “Composition A lotion”

72 subjects “Tazorac® 0.1% cream”

34 subjects “Lotion Placebo”

35 subjects “Cream Placebo”.

[0055] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 40, and non-inflammatory lesion count of at least 20 but no more than 100. The blindly labeled lotions were applied to the affected area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0056] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score (EGSS), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0057] Clinical Efficacy was determined primarily based on the percentage of subjects who were treatment successes at 12 weeks. To be judged as a treatment success, as reported in Tables 4, 6, and 7, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to "clear" or "almost clear". Also, the numbers of inflammatory and non-inflammatory lesions were assessed.

[0058] Table 3 reports Baseline Characteristics.

Table 3
Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory lesions

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Inflammatory Lesions			
Mean (SD)	27.2 (5.49)	28.3 (6.0)	27.3 (5.95)
Median	26.0	27.0	26.0
Non-inflammatory Lesions			
Mean (SD)	36.6 (13.17)	37.6 (14.70)	36.6 (13.31)
Median	34.0	34.0	34.0

[0059] Table 4 reports treatment % success on an intention-to-treat (ITT) basis.

Table 4
EGSS (Clear or Almost Clear) by Visit (ITT)

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	0%	0%	0%
Week 4	0%	1.4%	1.4%
Week 8	4.3%	7.2%	5.6%
Week 12	10.1%	18.8%	16.7%

[0060] Table 5 reports absolute change in inflammatory lesions from baseline.

Change in inflammatory and non-inflammatory lesions from baseline is reported in Figures 2 and 3.

Table 5
Inflammatory Lesions by Visit
Absolute Change from Baseline

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	-4.7	-2.9	-2.4
Week 4	-7.2	-5.8	-7.8
Week 8	-10.9	-13.2	-12.0
Week 12	-14.0	-18.1	-16.8

[0061] Table 6 reports treatment % success for primary efficacy on an intention-to-treat basis for EGSS at week 12. For EGSS, to be judged as a treatment success, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to “clear” or “almost clear”. For inflammatory and non-inflammatory lesions, absolute change from baseline to week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 6
Treatment % Success (ITT) at 12 Weeks

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
EGSS – Clear or Almost Clear	10.1%	18.8%	16.7%
Inflammatory Lesions Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

[0062] Table 7 reports treatment % success on a per-protocol basis for EGSS. For lesions, absolute change from baseline to Week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 7
Treatment % Success (PP)

	Combined Placebo N=57	Composition A N=54	Tazorac® 0.1% Cream N=56
EGSS – Clear or Almost Clear	12.3%	20.4%	16.1%
Inflammatory Lesions	-14.2	-18.3	-18.2
Non-inflammatory Lesions	-11.8	-20.8	-21.9

[0063] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by burning, stinging or itching reported by the subjects. This data is summarized in Figures 4A, 4B, and 4C. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation and hyper-pigmentations as evaluated by the investigator. This data is summarized in Figures 5A, 5B, 5C, and 5D.

[0064] Table 8 reports treatment emergent adverse event characteristics.

Table 8
Treatment Emergent Adverse Event Characteristics

	Combined Placebo	Composition A	Tazorac® 0.1% Cream
% Subjects Reporting Any Adverse Event	13.4%	14.7%	26.8%
% Subjects Reporting Any Serious Adverse Event	0%	0%	0%
% Subjects Discontinued Study Due to Adverse Event	0%	0%	1.4%

[0065] Notably, this clinical study showed that Composition A, containing less than half of the tazarotene active ingredient, had a numerically better efficacy than the Tazorac® 0.1% Cream. Also, the adverse event profile was lower for Composition A than for Tazorac® 0.1% Cream.

[0066] In another aspect, the present invention provides a method for treating acne. The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more times per day for a period of time sufficient to treat such acne. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days. Alternatively, it may be applied two or three times per day for 7-14 days. Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

[0067] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4

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weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

[0068] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene.

[0069] Two larger clinical studies (Studies 301 and 302) in acne patients were conducted to compare the efficacy of a composition of the present invention containing tazarotene (the "Composition A" Lotion of Table 2) to that of a placebo that was the vehicle of Composition A (i.e., without the active ingredient tazarotene).

[0070] These studies were phase-3, multi-center, randomized, double-blind, vehicle-controlled, two-arm, parallel group studies comparing the safety and efficacy of Composition A ("IDP-123 Lotion" or "Composition A Lotion") and IDP-123 vehicle lotion ("Placebo Lotion") in the treatment of acne vulgaris. Neither the acne patient nor the investigator knew the identity of the test composition assigned.

[0071] In the first study (Study 301), 813 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

402 subjects receiving "Composition A Lotion,"

411 subjects receiving "Placebo Lotion."

[0072] In the second study (Study 302), 801 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

397 subjects receiving "Composition A Lotion,"

404 subjects receiving "Placebo Lotion."

[0073] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 50, and non-inflammatory lesion count of at least 25 but no more than 100. The blindly labeled lotions were applied to the affected facial area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0074] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score ("EGSS"), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0075] Clinical Efficacy was determined primarily based on: (1) superiority in absolute change from baseline to week 12 in mean inflammatory counts; (2) superiority in absolute change from baseline to week 12 in mean non-inflammatory counts; and (3) percentage of subjects who achieve at least a two-grade reduction from baseline and are "Clear" or "Almost Clear" at week 12 in the EGSS.

[0076] Table 9 reports Baseline Characteristics.

Table 9

Subject Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory Lesion Counts

	Study 301		Study 302	
	Composition A Lotion N=402 ⁽¹⁾	Placebo Lotion N=411 ⁽¹⁾	Composition A Lotion N=397 ⁽¹⁾	Placebo Lotion N=404 ⁽¹⁾
Inflammatory Lesions				
Mean (SD)	28.5(7.04)	28.1 (7.04)	28.0 (7.32)	27.9 (7.10)
Median	26.0	26.0	26.0	26.0
Non-inflammatory Lesions				
Mean (SD)	41.1 (15.67)	40.7 (16.29)	41.8 (17.87)	40.6 (16.31)
Median	36.0	34.0	36.0	35.0

[0077] Table 10 reports treatment % success at week 12 on an intention-to-treat (ITT) basis.

Table 10
EGSS (Clear or Almost Clear) at Week 12 (ITT)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Week 12	25.5% (p<0.001)	13.0%	29.6% (p<0.001)	17.3

[0078] Table 11 reports absolute changes in inflammatory and non-inflammatory lesions from baseline at week 12.

Table 11
Inflammatory and Non-Inflammatory Lesions
Absolute Changes from Baseline at Week 12

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Inflammatory Lesions	-15.6 (p<0.001)	-12.4	-16.7 (p<0.001)	-13.4
Non-inflammatory Lesions	-21.0 (p<0.001)	-16.4	-24.6 (p<0.001)	-16.6

[0079] Table 12 reports assessment of treatment success on a per-protocol basis for EGSS. For lesions, absolute changes from baseline to week 12 in mean inflammatory and non-inflammatory counts are reported.

Table 12
Treatment Success (Per-Protocol Basis)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
EGSS – Clear or Almost Clear	26.8%	14.4%	30.6%	18.3%
Inflammatory Lesions	-15.8	-12.4	-16.4	-13.4
Non-inflammatory Lesions	-21.3	-16.3	-24.1	-15.4

[0080] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by itching, burning, or stinging reported by the subjects. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentations, as evaluated by the investigator.

[0081] Table 13 shows the number of subjects reporting moderate or severe itching, burning, or stinging; or being observed to have moderate or severe scaling, erythema, hypopigmentation, or hyperpigmentation. In general, the reported numbers of these conditions are similar between those subjects using Composition A Lotion and Placebo Lotion.

Table 13

Cutaneous Safety and Tolerability

	Study 301		Study 302	
	Composition A Lotion N=387	Placebo Lotion N=392	Composition A Lotion N=392	Placebo Lotion N=399
Scaling				
Moderate	4	2	6	1
Severe	0	0	1	0
Erythema				
Moderate	7	8	13	6
Severe	0	0	1	0
Hypopigmentation				
Moderate	1	1	0	0
Severe	0	0	0	0
Hyperpigmentation				
Moderate	7	9	8	17
Severe	1	2	0	1
Itching				
Moderate	4	2	4	4
Severe	0	0	0	0
Burning				
Moderate	2	0	5	0
Severe	0	0	2	0
Stinging				
Moderate	1	1	3	0
Severe	0	0	1	0

[0082] Table 13 reports treatment emergent adverse event characteristics.

Table 13

Treatment Emergent Adverse Event Characteristics

	Study 301		Study 302	
	Composition A Lotion N=392 ⁽¹⁾	Placebo Lotion N=399 ⁽¹⁾	Composition A Lotion N=387 ⁽¹⁾	Placebo Lotion N=392 ⁽¹⁾
% Subjects Reporting Any Adverse Event	25.5%	19.5%	28.2%	18.6%
% Subjects Reporting Any Serious Adverse Event	0.8%	0.8%	0.3%	0.3%
% Subjects Discontinued Study Due to Adverse Event	3.1%	0.5%	2.6%	0.5%

Note: (1) safety population, which comprises all randomized subjects who were presumed to have used the study drug at least once and who provided at least one post-baseline safety evaluation.

[0083] Notably, these clinical studies showed that the percentages of subjects reporting any serious adverse event for Composition A are no higher than those for the Placebo Lotion, indicating the excellent safety of Composition A.

[0084] The treatment success, as measured by investigator's global assessment of Composition A Lotion (denoted as "EGSS" above) and some commercial products containing a retinoid (as gleaned from their package inserts) is shown in Table 14.

Table 14

Comparison of Treatment Success of Various Products Containing a Retinoid

		Number of Subjects	Treatment Success (%)
Tazarotene Products	Composition A Lotion, 0.045% tazarotene	402	25.5
		397	29.6
	Tazorac Cream, 0.1% tazarotene	218	18
		206	20
	Fabior Foam, 0.1% tazarotene	371	29
		373	28
Tretinoin Products	Altreno Lotion, 0.05% tretinoin	406	16.5
		413	19.8
	Atralin Gel, 0.05% tretinoin	375	21
		299	23
Adapalene Products	Adapalene Gel, 0.3%	258	21
	Adapalene Gel, 0.1%	261	16
	Adapalene Lotion, 0.1%	533	26.3
		535	24.1
	Epiduo Gel, 0.1% adapalene/2.5% benzoyl peroxide	149	21.5
		415	30.1
	0.1% Adapalene in Epiduo vehicle	148	12.2
		420	19.8

[0085] Surprisingly, Composition A Lotion achieved at least similar or higher success rate than other products that contain at least twice the concentration of the active ingredient.

[0086] In another aspect, the present invention provides a method for treating acne vulgaris (acne). The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more (such as 1, 2, 3, or more) times per day for a period of time sufficient to treat such acne vulgaris. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days.

Alternatively, it may be applied two or three times per day for 7-14 days.

Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

[0087] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

[0088] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene (Tazorac® Cream).

[0089] While the present disclosure shows and describes a number of exemplary embodiments, it will be manifest to those skilled in the art that various further modifications may be made without departing from the spirit and scope of

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the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of U.S. Patent Application No. 15/173,961, filed June 6, 2016, which claims priority to U.S. Provisional Patent 62/181,481, filed June 18, 2015; and this application is a continuation-in-part application of U.S. Patent Application No. 15/977,088, filed May 11, 2018, which claims priority to U.S. Provisional Patent 62/505,421, filed May 12, 2017.

[0002]

BACKGROUND

[0003] The present invention relates to topical compositions and methods for treating skin diseases such as acne and psoriasis. In particular, this invention relates to topical pharmaceutical compositions comprising tazarotene or a pharmaceutically acceptable tazarotenic acid salt, in an oil-in-water emulsion vehicle, for treating skin diseases.

[0004] The retinoid tazarotene has been commercially available and has been used to treat acne and psoriasis topically. However, tazarotene may cause significant local skin irritation, especially early in the first through fourth weeks of therapy, thus limiting its use for a prolonged period because many patients stop treatment due to skin irritation. The need exists for more effective and safer topical

medicaments with reduced adverse effects for the management of acne, psoriasis and other skin diseases.

SUMMARY OF THE INVENTION

[0005] In general, the present invention provides topical compositions and methods for treating skin diseases such as acne and psoriasis.

[0006] In one aspect, this invention provides a topical pharmaceutical composition for treating skin diseases, including acne and psoriasis, comprising: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0007] In another aspect, this invention provides a method of treating skin diseases, including acne and psoriasis, comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from the skin disease, wherein the composition comprises: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0008] According to other aspects, the topical pharmaceutical composition may comprise tazarotene or the salt thereof at 0.01 to 0.049 percent by weight of the composition, or at about 0.045 percent by weight of the composition.

[0009] According to another aspect, the tazarotene or tazarotenic acid salt may be dissolved in a liquid oil component of the emulsion.

[0010] According to another aspect, the topical pharmaceutical composition may contain the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.

[0011] According to various aspects, the oil phase of the emulsion may comprise a liquid oil component comprising a DCAE, a MCAE, or combinations thereof. In other aspects, the oil phase includes diethyl sebacate as the DCAE.

[0012] According to other aspects, the aqueous phase of the emulsion may comprise water and a carbomer homopolymer.

[0013] According to another aspect, the topical pharmaceutical composition may comprise: an aqueous phase comprising water, a carbomer homopolymer, and a polymeric emulsifier; an oil phase comprising at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil, and the tazarotene or the tazarotenic acid salt. According to other aspects, the aqueous phase may further comprise a humectant or a preservative, such as at least one member selected from the group consisting of methylparaben, propylparaben and sorbitol.

[0014] According to other aspects, the topical pharmaceutical composition may have the form of a lotion, or of a cream.

[0015] According to another aspect, the topical pharmaceutical composition may have a pH of about 4 to about 6.

[0016] For the methods of this invention, the step of applying may be carried out once per day for at least eight weeks. According to one aspect, the applying is carried out once per day for at least twelve weeks.

[0017] According to other aspects, the composition may be applied is to an affected area of a body of a subject suffering from acne vulgaris in order to treat that condition.

[0018] Other features and advantages of the present invention will become apparent from the accompanying drawings and the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

[0019] Figure 1 is a graph of EGSS by visit.

[0020] Figure 2 is a graph of change in inflammatory lesions from baseline.

[0021] Figure 3 is a graph of change in non-inflammatory lesions from baseline.

[0022] Figures 4A, 4B, and 4C are graphs of cutaneous tolerability to burning, stinging, and itching, respectively.

[0023] Figures 5A, 5B, 5C, and 5D are graphs of cutaneous safety assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentation, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0024] In general, the present invention provides topical compositions and methods for treating skin diseases, including acne and psoriasis.

[0025] Throughout this disclosure, unless otherwise indicated, the concentration of an ingredient of the composition is in percent by weight of the total composition.

[0026] In one aspect, the topical pharmaceutical composition comprises tazarotene, or a pharmaceutically acceptable salt of tazarotenic acid, at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or the tazarotenic acid salt is included in a composition at a positive concentration less than 0.05 wt%.

[0027] In certain embodiments of the present invention, tazarotene or the tazarotenic acid salt is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition ("wt%"). For example, this component is present in the range from about 0.01 to about 0.049 wt%, or from about 0.01 to about 0.045 wt%, or from about 0.02 to about 0.045 wt%, or from about 0.03 to about 0.045 wt%, or at about 0.045 wt%. Specific concentrations of this component may be 0.01 wt%, 0.015 wt%, 0.02 wt%, 0.025 wt%, 0.03 wt%, 0.035 wt%, 0.04 wt%, and 0.045 wt%.

[0028] In one aspect, the topical pharmaceutical composition comprises an oil-in-water emulsion as a carrier vehicle, in which an internal oil phase is dispersed in a continuous aqueous phase. The emulsion may be a macroemulsion, a

microemulsion, or a nanoemulsion. The composition may have the dosage form of gel, lotion, or cream, or ointment, or liquid, or oil, or spray or foam.

[0029] In addition to the tazarotene active ingredient, the composition of the present invention may comprise one or more dermatologically acceptable excipients, such as liquid oils, waxes viscosity-modifying agents, thickening agents, gelling agents, alcohols, surfactants, chelating agents, buffers, preservatives, humectants, emollients, stabilizers, diluents, dispersing agents, emulsifiers, wetting agents, stabilizers, pH adjusters, solvents or cosolvents.

[0030] The composition of the invention may desirably contain a thickening agent to provide viscosity so that the formulation may be provided in the form of a gel, lotion, cream, or ointment. The thickening agent may be miscible or soluble in an aqueous fluid. Non-limiting examples of suitable thickening agents include acacia, alginic acid and its salts, hyaluronic acid and its salts, carbomers (also known as carboxy vinyl polymers, which are cross-linked polyacrylic acid), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohol, tragacanth, xanthan gum, magnesium aluminum silicate, and bentonite. The thickening agent may also reside in the oil or lipophilic portion of the formulation. Examples of suitable lipophilic thickening agents include cetyl alcohol, stearyl alcohol, glyceryl stearate, white beeswax, microcrystalline wax, hydrogenated polyisobutane polymers, and emulsifying wax.

[0031] A suitable group of thickening agents is carbomers, such as Carbopol® and polycarbophil (The Lubrizol Corporation, Wickliffe, Ohio). Carbopol® homopolymers are polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol. Carbopol® copolymers are polymers of acrylic acid and C₁₀-C₃₀ alkyl acrylate crosslinked with allylpentaerythritol. Carbopol® interpolymers are carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester. Noveon® polycarbophil is a polymer of acrylic acid crosslinked with divinyl glycol.

[0032] A surfactant or emulsifier is optionally included, if desired or required. Pharmaceutically acceptable anionic, cationic, or non-ionic surfactants may be included in a composition of the present invention. Non-ionic surfactants are preferred. Non-limiting examples of non-ionic surfactants are Octoxynol (also known as Macrogol tetramethylbutylphenyl ether, octylphenoxy polyethoxyethanol, or polyoxyethylene octylphenyl ether), such as Octoxynol 1, 3, 5, 8, 9, 10, 12, 13, 16, 30, 40, 70 (wherein the number indicates the number of repeating oxyethylene units), or other Octoxynols that comprise different numbers of repeating units of oxyethylene in the side chain, sorbitan esters (such as sorbitan monooleate and sorbitan monostearate, commonly known by their trade names Span 80 and Span 60), polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade

names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc.), other nonionic surfactants such as Brij® (polyoxyethylene alkyl ether having a formula of $\text{CH}_3-(\text{CH}_2)_{10-18}-(\text{O}-\text{C}_2\text{H}_4)_{1-25}-\text{OH}$), Myrj® (stearic acid esterified with polyoxyethylene having 40-100 repeating oxyethylene units), and long chain fatty alcohols (e.g., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosahexaenoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms).

[0033] In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used. These are polymers of acrylic acid, modified by long chain (C₁₀-C₃₀) alkyl acrylates, and crosslinked with allylpentaerythritol.

[0034] An anionic emulsifier may be used, such as sodium or potassium oleate, triethanolamine stearate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Still other emulsifiers include glyceryl monostearate, polyoxyethylene monooleate, polyoxyethylene monostearate, polyoxyethylene monolaurate, potassium oleate, sodium lauryl sulfate, sodium oleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, triethanolamine oleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene

sorbitan monostearate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monooleate, and polyoxyethylene sorbitan trioleate.

[0035] The formulation desirably contains a dermatologically acceptable humectant such as glycerin, sorbitol, hexylene glycol, propylene glycol, or urea. In addition, the formulation may contain an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. Chelating agents such as EDTA and citric acid and their salts may be included in a formulation of the present invention.

[0036] The liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature. For example, in one embodiment, the liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature of 22 °C. The liquid oil component may be selected from one or more ingredients from the group consisting of dicarboxylic acid esters ("DCAE"), monocarboxylic acid esters ("MCAE"), fish-liver oil, long-chain triglycerides (wherein each side chain has 14-18 carbons, such as peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, olive oil, cotton seed oil, or derivatives thereof), propylene glycol diesters, medium-chain triglycerides (such as those wherein each side chains has 8-10 carbons; e.g., capric/caprylic acid triglycerides), hydrocarbons like mineral oil, light mineral oil, squalene, and squalane, fatty alcohols (such as octyldodecanol and isostearyl alcohol), and fatty acids (such as isostearic acid and oleic acid).

[0037] In some embodiments, the liquid oil component comprises a dicarboxylic acid ester and light mineral oil. In some other embodiments, the liquid oil component comprises one or more long-chain triglycerides.

[0038] The formulation may include other lipophilic liquids in an amount that is sufficient to be miscible with the dicarboxylic acid ester and/or monocarboxylic acid ester. The lipophilic liquid may be an emollient such as lanolin oil, mineral oil, light mineral oil, isostearic acid, squalene, octyldodecanol, fractionated coconut oil, cyclomethicone, or dimethicone.

[0039] In addition to the liquid oil component, the formulation may contain water insoluble or practically insoluble ingredients that are not liquid at room temperature, but are soluble in the liquid oil component.

[0040] A DCAE that is suitable for the present invention has the formula $R_1OOC-(CH_2)_n-COOR_2$, wherein R_1 and R_2 are alkyl groups containing between 1 and 4 carbons or aryl groups and may be the same or may be different and wherein $(CH_2)_n$ is a straight or branched chain and n is between 1 and 12. Examples of DCAEs containing one or more aryl groups are dibenzyl esters of dicarboxylic acids. A preferred dicarboxylic acid ester is diethyl sebacate, which has the formula $CH_3CH_2OOC-(CH_2)_8-COOCH_2CH_3$. Examples of other suitable dicarboxylic acid esters (where R_1 and R_2 are the same) are dimethyl, diethyl, dipropyl, diisopropyl, dibutyl and diisobutyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, and azalate. Examples of suitable dicarboxylic acid esters (where R_1 is different from R_2) are methyl ethyl, methyl propyl, methyl butyl, methyl

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isopropyl, ethyl propyl, ethyl butyl, ethyl isopropyl, and propyl butyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, azalate, and sebacate.

[0041] In some aspects, diethyl sebacate is included at 0.1 to 20 wt%, or at 0.5 to 10 wt%, or at 2 to 4 wt% of the weight of the composition.

[0042] Alternatively, or in combination with the DCAE, the formulation may contain a MCAE. The MCAE that is suitable for the present invention has the formula $\text{CH}_3-(\text{CH}_2)_n-\text{COOR}_1$, wherein R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and wherein $(\text{CH}_2)_n$ is straight or branched chain and n is between 1 and 12. Examples of such monocarboxylic acid esters include methyl, ethyl, propyl, isopropyl, butyl, or an aryl such as benzyl formate, acetate, propionate, butyrate, valerate, laurate, myristate, palmitate, and stearate. Examples of preferred monocarboxylic acid esters are isopropyl palmitate and isopropyl myristate.

[0043] The liquid oil phase may beneficially be used to dissolve one or more of the active ingredients within the emulsion. In one embodiment the tazarotene component is dissolved in the liquid oil phase within the formulation at room temperature. In another embodiment the tazarotene component is suspended within the formulation at room temperature. In the case wherein the tazarotene component is suspended in the formulation, this suspended active ingredient may be micronized, namely that the mean particle size is preferably about 25 microns in diameter or less.

[0044] In one aspect, a composition of the present invention comprises the ingredients at the concentrations shown in Table 1.

Table 1

Compositions of the Present Invention for Treating Skin Diseases

Ingredient	Concentration (wt%)		
	Range 1	Range 2	Range 3
Tazarotene or Tazarotenic Acid Compound	0.01-0.049	0.02-0.045	0.03-0.045
Emollient, Solvent, and/or Thickener	0.5-40	1-25	2-20
Emulsifier	0.25-10	0.5-7	1-5
Humectant	0-15	2-12	3-10
Polymeric Thickener	0.05-2	0.1-1.5	0.3-1
Pharmaceutical Aids	q.s.	q.s.	q.s.
Purified water	q.s. to 100	q.s. to 100	q.s. to 100

[0045] Non-limiting examples of compositions of the present invention are shown in Table 2.

Table 2

Some Emulsion Compositions of the Present Invention for Treating Acne

Ingredient	Function	Concentration (wt%)			
		Range 1	Range 2	Range 3	Composition A
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Note: ⁽¹⁾ These ingredients are broadly classified as Pharmaceutical Aids.

[0046] A lotion having a composition as shown Composition A of Table 2 may be prepared as follows.

[0047] A separate aqueous phase is made. In a manufacturing vessel equipped with a mixing implement (such as a propeller) and temperature control, purified

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water and disodium edetate dihydrate are combined and the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and heated to approximately 75 °C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40 °C with continued mixing. With continuous mixing, Carbopol® 981 and Pemulen™ TR-1 carbomers are added to the mixture and dispersed. Mixing continues until the two carbomers are fully dispersed and hydrated.

[0048] A separate oil phase is made. In a vessel equipped with a mixing implement such as a propeller, diethyl sebacate, and tazarotene are combined. The mixture is agitated until a solution is achieved. With continuous mixing, light mineral oil and sorbitan monooleate are added. Mixing is continued until a solution is obtained.

[0049] In a separate vessel, an approximate 2.5 N solution of sodium hydroxide is prepared.

[0050] With high speed mixing, the oil phase containing the active ingredient (tazarotene) is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Mixing speed is decreased and mixing continued for an additional time of 10 minutes to 1 hour. With continuous mixing, an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5 ± 0.5 . Mixing continues further until a homogeneous lotion is obtained, such as for 30 minutes to 3 hours.

[0051] A first clinical study in acne patients was conducted to compare the efficacy of a composition of the present invention containing tazarotene (the “Composition A” lotion of Table 2).

[0052] A first placebo (“Lotion Placebo”) corresponded to and had a similar viscosity as Composition A but lacked tazarotene. A second placebo (“Cream Placebo”) corresponded to the Lotion Placebo but employed carbomer homopolymer type C in place of carbomer homopolymer type A to yield a higher viscosity emulsion with a viscosity similar to 0.1% tazarotene cream employed in the study. This allows for better blinding of the test formulations and control of the clinical study. In the following results, data for Lotion Placebo and Cream Placebo may be combined and reported as “Combined Placebo”.

[0053] Additionally, commercially available 0.1% tazarotene cream (Tazorac® 0.1% cream) was employed in this clinical study for comparison purposes.

[0054] A double blind, multi-site, randomized clinical study was conducted on patients suffering from acne vulgaris, whereby neither the acne patient nor the investigator knew the identity of the test composition assigned. 210 patients were randomized to receive either Composition A lotion, Tazorac® 0.1% cream, Placebo Lotion and Placebo Cream at a 2:2:1:1 randomization:

69 subjects “Composition A lotion”

72 subjects “Tazorac® 0.1% cream”

34 subjects “Lotion Placebo”

35 subjects “Cream Placebo”.

[0055] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 40, and non-inflammatory lesion count of at least 20 but no more than 100. The blindly labeled lotions were applied to the affected area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0056] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score (EGSS), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0057] Clinical Efficacy was determined primarily based on the percentage of subjects who were treatment successes at 12 weeks. To be judged as a treatment success, as reported in Tables 4, 6, and 7, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to "clear" or "almost clear". Also, the numbers of inflammatory and non-inflammatory lesions were assessed.

[0058] Table 3 reports Baseline Characteristics.

Table 3
Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory lesions

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Inflammatory Lesions			
Mean (SD)	27.2 (5.49)	28.3 (6.0)	27.3 (5.95)
Median	26.0	27.0	26.0
Non-inflammatory Lesions			
Mean (SD)	36.6 (13.17)	37.6 (14.70)	36.6 (13.31)
Median	34.0	34.0	34.0

[0059] Table 4 reports treatment % success on an intention-to-treat (ITT) basis.

Table 4
EGSS (Clear or Almost Clear) by Visit (ITT)

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	0%	0%	0%
Week 4	0%	1.4%	1.4%
Week 8	4.3%	7.2%	5.6%
Week 12	10.1%	18.8%	16.7%

[0060] Table 5 reports absolute change in inflammatory lesions from baseline. Change in inflammatory and non-inflammatory lesions from baseline is reported in Figures 2 and 3.

Table 5
Inflammatory Lesions by Visit
Absolute Change from Baseline

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	-4.7	-2.9	-2.4
Week 4	-7.2	-5.8	-7.8
Week 8	-10.9	-13.2	-12.0
Week 12	-14.0	-18.1	-16.8

[0061] Table 6 reports treatment % success for primary efficacy on an intention-to-treat basis for EGSS at week 12. For EGSS, to be judged as a treatment success, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to “clear” or “almost clear”. For inflammatory and non-inflammatory lesions, absolute change from baseline to week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 6
Treatment % Success (ITT) at 12 Weeks

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
EGSS – Clear or Almost Clear	10.1%	18.8%	16.7%
Inflammatory Lesions Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

[0062] Table 7 reports treatment % success on a per-protocol basis for EGSS. For lesions, absolute change from baseline to Week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 7
Treatment % Success (PP)

	Combined Placebo N=57	Composition A N=54	Tazorac® 0.1% Cream N=56
EGSS – Clear or Almost Clear	12.3%	20.4%	16.1%
Inflammatory Lesions	-14.2	-18.3	-18.2
Non-inflammatory Lesions	-11.8	-20.8	-21.9

[0063] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by burning, stinging or itching reported by the subjects. This data is summarized in Figures 4A, 4B, and 4C. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation and hyper-pigmentations as evaluated by the investigator. This data is summarized in Figures 5A, 5B, 5C, and 5D.

[0064] Table 8 reports treatment emergent adverse event characteristics.

Table 8
Treatment Emergent Adverse Event Characteristics

	Combined Placebo	Composition A	Tazorac® 0.1% Cream
% Subjects Reporting Any Adverse Event	13.4%	14.7%	26.8%
% Subjects Reporting Any Serious Adverse Event	0%	0%	0%
% Subjects Discontinued Study Due to Adverse Event	0%	0%	1.4%

[0065] Notably, this clinical study showed that Composition A, containing less than half of the tazarotene active ingredient, had a numerically better efficacy than the Tazorac® 0.1% Cream. Also, the adverse event profile was lower for Composition A than for Tazorac® 0.1% Cream.

[0066] In another aspect, the present invention provides a method for treating acne. The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more times per day for a period of time sufficient to treat such acne. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days. Alternatively, it may be applied two or three times per day for 7-14 days. Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

[0067] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4

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weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

[0068] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene.

[0069] Two larger clinical studies (Studies 301 and 302) in acne patients were conducted to compare the efficacy of a composition of the present invention containing tazarotene (the "Composition A" Lotion of Table 2) to that of a placebo that was the vehicle of Composition A (i.e., without the active ingredient tazarotene).

[0070] These studies were phase-3, multi-center, randomized, double-blind, vehicle-controlled, two-arm, parallel group studies comparing the safety and efficacy of Composition A ("IDP-123 Lotion" or "Composition A Lotion") and IDP-123 vehicle lotion ("Placebo Lotion") in the treatment of acne vulgaris. Neither the acne patient nor the investigator knew the identity of the test composition assigned.

[0071] In the first study (Study 301), 813 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

402 subjects receiving "Composition A Lotion,"

411 subjects receiving "Placebo Lotion."

[0072] In the second study (Study 302), 801 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

397 subjects receiving "Composition A Lotion,"

404 subjects receiving "Placebo Lotion."

[0073] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 50, and non-inflammatory lesion count of at least 25 but no more than 100. The blindly labeled lotions were applied to the affected facial area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0074] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score ("EGSS"), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0075] Clinical Efficacy was determined primarily based on: (1) superiority in absolute change from baseline to week 12 in mean inflammatory counts; (2) superiority in absolute change from baseline to week 12 in mean non-inflammatory counts; and (3) percentage of subjects who achieve at least a two-grade reduction from baseline and are "Clear" or "Almost Clear" at week 12 in the EGSS.

[0076] Table 9 reports Baseline Characteristics.

Table 9

Subject Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory Lesion Counts

	Study 301		Study 302	
	Composition A Lotion N=402 ⁽¹⁾	Placebo Lotion N=411 ⁽¹⁾	Composition A Lotion N=397 ⁽¹⁾	Placebo Lotion N=404 ⁽¹⁾
Inflammatory Lesions				
Mean (SD)	28.5(7.04)	28.1 (7.04)	28.0 (7.32)	27.9 (7.10)
Median	26.0	26.0	26.0	26.0
Non-inflammatory Lesions				
Mean (SD)	41.1 (15.67)	40.7 (16.29)	41.8 (17.87)	40.6 (16.31)
Median	36.0	34.0	36.0	35.0

[0077] Table 10 reports treatment % success at week 12 on an intention-to-treat (ITT) basis.

Table 10
EGSS (Clear or Almost Clear) at Week 12 (ITT)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Week 12	25.5% (p<0.001)	13.0%	29.6% (p<0.001)	17.3

[0078] Table 11 reports absolute changes in inflammatory and non-inflammatory lesions from baseline at week 12.

Table 11
Inflammatory and Non-Inflammatory Lesions
Absolute Changes from Baseline at Week 12

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Inflammatory Lesions	-15.6 (p<0.001)	-12.4	-16.7 (p<0.001)	-13.4
Non-inflammatory Lesions	-21.0 (p<0.001)	-16.4	-24.6 (p<0.001)	-16.6

[0079] Table 12 reports assessment of treatment success on a per-protocol basis for EGSS. For lesions, absolute changes from baseline to week 12 in mean inflammatory and non-inflammatory counts are reported.

Table 12
Treatment Success (Per-Protocol Basis)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
EGSS – Clear or Almost Clear	26.8%	14.4%	30.6%	18.3%
Inflammatory Lesions	-15.8	-12.4	-16.4	-13.4
Non-inflammatory Lesions	-21.3	-16.3	-24.1	-15.4

[0080] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by itching, burning, or stinging reported by the subjects. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentations, as evaluated by the investigator.

[0081] Table 13 shows the number of subjects reporting moderate or severe itching, burning, or stinging; or being observed to have moderate or severe scaling, erythema, hypopigmentation, or hyperpigmentation. In general, the reported numbers of these conditions are similar between those subjects using Composition A Lotion and Placebo Lotion.

Table 13

Cutaneous Safety and Tolerability

	Study 301		Study 302	
	Composition A Lotion N=387	Placebo Lotion N=392	Composition A Lotion N=392	Placebo Lotion N=399
Scaling				
Moderate	4	2	6	1
Severe	0	0	1	0
Erythema				
Moderate	7	8	13	6
Severe	0	0	1	0
Hypopigmentation				
Moderate	1	1	0	0
Severe	0	0	0	0
Hyperpigmentation				
Moderate	7	9	8	17
Severe	1	2	0	1
Itching				
Moderate	4	2	4	4
Severe	0	0	0	0
Burning				
Moderate	2	0	5	0
Severe	0	0	2	0
Stinging				
Moderate	1	1	3	0
Severe	0	0	1	0

[0082] Table 13 reports treatment emergent adverse event characteristics.

Table 13

Treatment Emergent Adverse Event Characteristics

	Study 301		Study 302	
	Composition A Lotion N=392 ⁽¹⁾	Placebo Lotion N=399 ⁽¹⁾	Composition A Lotion N=387 ⁽¹⁾	Placebo Lotion N=392 ⁽¹⁾
% Subjects Reporting Any Adverse Event	25.5%	19.5%	28.2%	18.6%
% Subjects Reporting Any Serious Adverse Event	0.8%	0.8%	0.3%	0.3%
% Subjects Discontinued Study Due to Adverse Event	3.1%	0.5%	2.6%	0.5%

Note: (1) safety population, which comprises all randomized subjects who were presumed to have used the study drug at least once and who provided at least one post-baseline safety evaluation.

[0083] Notably, these clinical studies showed that the percentages of subjects reporting any serious adverse event for Composition A are no higher than those for the Placebo Lotion, indicating the excellent safety of Composition A.

[0084] The treatment success, as measured by investigator's global assessment of Composition A Lotion (denoted as "EGSS" above) and some commercial products containing a retinoid (as gleaned from their package inserts) is shown in Table 14.

Table 14

Comparison of Treatment Success of Various Products Containing a Retinoid

		Number of Subjects	Treatment Success (%)
Tazarotene Products	Composition A Lotion, 0.045% tazarotene	402	25.5
		397	29.6
	Tazorac Cream, 0.1% tazarotene	218	18
		206	20
	Fabior Foam, 0.1% tazarotene	371	29
		373	28
Tretinoin Products	Altreno Lotion, 0.05% tretinoin	406	16.5
		413	19.8
	Atralin Gel, 0.05% tretinoin	375	21
		299	23
Adapalene Products	Adapalene Gel, 0.3%	258	21
	Adapalene Gel, 0.1%	261	16
	Adapalene Lotion, 0.1%	533	26.3
		535	24.1
	Epiduo Gel, 0.1% adapalene/2.5% benzoyl peroxide	149	21.5
		415	30.1
	0.1% Adapalene in Epiduo vehicle	148	12.2
		420	19.8

[0085] Surprisingly, Composition A Lotion achieved at least similar or higher success rate than other products that contain at least twice the concentration of the active ingredient.

[0086] In another aspect, the present invention provides a method for treating acne vulgaris (acne). The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more (such as 1, 2, 3, or more) times per day for a period of time sufficient to treat such acne vulgaris. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days.

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Alternatively, it may be applied two or three times per day for 7-14 days.

Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

[0087] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

[0088] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene (Tazorac® Cream).

[0089] While the present disclosure shows and describes a number of exemplary embodiments, it will be manifest to those skilled in the art that various further modifications may be made without departing from the spirit and scope of

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the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

Electronic Patent Application Fee Transmittal				
Application Number:		16179576		
Filing Date:		02-Nov-2018		
Title of Invention:		TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		
First Named Inventor/Applicant Name:		Angel Arturo		
Filer:		Andrew James Anderson/Bethany Weber		
Attorney Docket Number:		99336.000207-CIP		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	3	100	300
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				460

Electronic Acknowledgement Receipt	
EFS ID:	34981718
Application Number:	16179576
International Application Number:	
Confirmation Number:	1093
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Angel Arturo
Customer Number:	134756
Filer:	Andrew James Anderson/Bethany Weber
Filer Authorized By:	Andrew James Anderson
Attorney Docket Number:	99336.000207-CIP
Receipt Date:	28-JAN-2019
Filing Date:	02-NOV-2018
Time Stamp:	16:40:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$460
RAM confirmation Number	012919INTEFSW00004120033875
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		99336-342_Response_Notice_File_Corrected_Papers.pdf	110831	yes	3
			21b987414d8bf0bf4d4dbcb11324034b89b4a4464a		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Response to Pre-Exam Formalities Notice		1	1	
	Specification		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	3	
Warnings:					
Information:					
2	Specification	99336-342-CIP_Spec_Marked-UP.pdf	210729	no	29
			715d06a6e5413275562aa6e0ccdd248c5553492		
Warnings:					
Information:					
3	Specification	99336-342-CIP_Sub_Spec_Clean_Copy.pdf	211370	no	29
			3abcb967c8cb25b2339b7fad508826dbddcb78ca		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32462	no	2
			5f1502df250bf64775aaa42398caf26e2de76ba		
Warnings:					
Information:					
Total Files Size (in bytes):			565392		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/179,576	11/02/2018	1629	1720	99336.000207-CIP	23	2

CONFIRMATION NO. 1093

FILING RECEIPT



0000000104045224

134756
HSE/Valeant
1600 Bausch & Lomb Place
Rochester, NY 14604

Date Mailed: 11/28/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Angel Arturo, Santa Rosa, CA;
Radhakrishnan Pillai, Santa Rosa, CA;

Applicant(s)

Valeant Pharmaceuticals North America, Bridgewater, NJ;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CIP of 15/977,088 05/11/2018
and is a CIP of 15/173,961 06/06/2016
and said 15/977,088 05/11/2018
claims benefit of 62/505,421 05/12/2017
and said 15/173,961 06/06/2016
claims benefit of 62/181,481 06/18/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/26/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/179,576**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
Title

TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

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countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/179,576	11/02/2018	Angel Arturo	99336.000207-CIP

CONFIRMATION NO. 1093

FORMALITIES LETTER



OC000000104045225

134756
HSE/Valeant
1600 Bausch & Lomb Place
Rochester, NY 14604

Date Mailed: 11/28/2018

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given **TWO MONTHS** from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
 - The application contains drawings, but the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(9).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Additional claim fees of \$ **300** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
The surcharge is due for any one of:
 - late submission of the basic filing fee, search fee, or examination fee,
 - late submission of inventor's oath or declaration,
 - filing an application that does not contain at least one claim on filing, or
 - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified

for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ **160** surcharge.
- \$ **300** for **3** total claims over 20.
- \$(**0**) previous unapplied payment amount.
- \$ **460** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Angel Arturo
Radhakrishnan Pillai

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

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/hachristian/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/179,576			
APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760		
TOTAL CLAIMS (37 CFR 1.16(i))	23	minus 20 = *	3			x 100 =	300		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	minus 3 = *				x 460 =	0.00		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL		TOTAL	2020		
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE					
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE					
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor	1					Remove	
Legal Name							
Prefix	Given Name	Middle Name		Family Name		Suffix	
	Angel			Arturo			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service							
City	Santa Rosa	State/Province	CA	Country of Residence	US		
Mailing Address of Inventor:							
Address 1		4953 Sheleen Court					
Address 2							
City	Santa Rosa	State/Province	CA				
Postal Code	95409	Country	US				
Inventor	2					Remove	
Legal Name							
Prefix	Given Name	Middle Name		Family Name		Suffix	
	Radhakrishnan			Pillai			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service							
City	Santa Rosa	State/Province	CA	Country of Residence	US		
Mailing Address of Inventor:							
Address 1		6787 Owl Hill Avenue					
Address 2							
City	Santa Rosa	State/Province	CA				
Postal Code	95409	Country	US				
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add							

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For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

☐ An Address is being provided for the correspondence information of this application.

Customer Number	134756		
Email Address	patent@hseclaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		
Attorney Docket Number	99336.000207-CIP	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	10	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:
☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	134756		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	15977088	2018-05-11
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	15173961	2016-06-06
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15977088	Claims benefit of provisional	62505421	2017-05-12
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15173961	Claims benefit of provisional	62181481	2015-06-18
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
			Access Code ⁱ (if applicable)
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant		1 Remove	
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear			
☒ Assignee		☐ Legal Representative under 35 U.S.C. 117	
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name		Valeant Pharmaceuticals North America	
Mailing Address Information For Applicant:			
Address 1		400 Somerset Corporate Boulevard	
Address 2			
City		Bridgewater	State/Province
Country		US	Postal Code
Phone Number			Fax Number
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button. Add			

Assignee Information including Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

Assignee 1				
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				Remove
If the Assignee or Non-Applicant Assignee is an Organization check here.				☐
Prefix	Given Name	Middle Name	Family Name	Suffix
Mailing Address Information For Assignee including Non-Applicant Assignee:				
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Phone Number		Fax Number		
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Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				Add

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Andrew J. Anderson/		Date (YYYY-MM-DD)	2018-11-02
First Name	Andrew J.	Last Name	Anderson	Registration Number
				33564
Additional Signature may be generated within this form by selecting the Add button.				Add

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	99336.000207-CIP
		Application Number	
Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

- 1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
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- 3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ABSTRACT

Topical pharmaceutical compositions include tazarotene or a pharmaceutically acceptable salt of tazarotenic acid and an oil-in-water emulsion vehicle that forms a lotion. The compositions are used to treat skin diseases, such as acne vulgaris.

[0090] WHAT IS CLAIMED IS:

1. A topical pharmaceutical composition for treating a skin disease, comprising:
tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a concentration in the range from about 0.01 to 0.049 percent by weight of the composition; and
a dermatologically acceptable oil-in-water emulsion vehicle; wherein said composition is a lotion.
2. The topical pharmaceutical composition of claim 1, comprising tazarotene at a concentration from about 0.03 to 0.049 percent by weight of the composition.
3. The topical pharmaceutical composition of claim 1, comprising tazarotene at a concentration of about 0.045 percent by weight of the composition.
4. The topical pharmaceutical composition of claim 1, wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion.
5. The topical pharmaceutical composition of claim 1, containing the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.
6. The topical pharmaceutical composition of claim 1, wherein an oil phase of the emulsion comprises a liquid oil component comprising a dicarboxylic acid ester ("DCAE"), a monocarboxylic acid ester ("MCAE"), or combinations thereof.
7. The topical pharmaceutical composition of claim 1, wherein an oil phase of the emulsion comprises diethyl sebacate.

8. The topical pharmaceutical composition of claim 1, wherein an aqueous phase of the emulsion comprises water and a carbomer homopolymer.
9. The topical pharmaceutical composition of claim 1, wherein an aqueous phase comprises water, a carbomer homopolymer, and a polymeric emulsifier; and wherein an oil phase comprises at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil.
10. The topical pharmaceutical composition of claim 1, wherein the oil phase comprises diethyl sebacate and mineral oil.
11. The topical pharmaceutical composition of claim 1, wherein the oil phase consists of diethyl sebacate and mineral oil.
12. The topical pharmaceutical composition of claim 1, having a pH of about 4 to about 6.
13. A method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from acne vulgaris; wherein the composition comprises:

tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a concentration from about 0.01 to 0.049 percent by weight of the composition; and

a dermatologically acceptable oil-in-water emulsion vehicle; wherein said composition is a lotion.

14. The method of claim 13, comprising tazarotene at a concentration from about 0.03 to 0.049 percent by weight of the composition.

15. The method of claim 13, comprising tazarotene at a concentration of about 0.045 percent by weight of the composition.

16. The method of claim 13, wherein said emulsion comprises:

an aqueous phase comprising water, a carbomer homopolymer, and a polymeric emulsifier; and

an oil phase comprising at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil.

17. The method of claim 16, wherein the oil phase of the emulsion comprises diethyl sebacate.

18. The method of claim 13, wherein the oil phase of the emulsion comprises diethyl sebacate and mineral oil.

19. The method of claim 13, wherein the oil phase of the emulsion consists of diethyl sebacate and mineral oil.

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20. The method of claim 13, wherein said applying is carried out once per day for at least eight weeks.

21. The method of claim 13, wherein said applying is carried out once per day for at least twelve weeks.

22. The method of claim 13, wherein said applying is carried out once per day for twelve weeks.

23. The method of claim 13, wherein the pharmaceutical composition contains the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.

TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of U.S. Patent Application No. 15/173,961, filed June 6, 2016, which claims priority to U.S. Provisional Patent 62/181,481, filed June 18, 2015; and this application is a continuation-in-part application of U.S. Patent Application No. 15/977,088, filed May 11, 2018, which claims priority to U.S. Provisional Patent 62/505,421, filed May 12, 2017.

[0002]

BACKGROUND

[0003] The present invention relates to topical compositions and methods for treating skin diseases such as acne and psoriasis. In particular, this invention relates to topical pharmaceutical compositions comprising tazarotene or a pharmaceutically acceptable tazarotenic acid salt, in an oil-in-water emulsion vehicle, for treating skin diseases.

[0004] The retinoid tazarotene has been commercially available and has been used to treat acne and psoriasis topically. However, tazarotene may cause significant local skin irritation, especially early in the first through fourth weeks of therapy, thus limiting its use for a prolonged period because many patients stop

treatment due to skin irritation. The need exists for more effective and safer topical medicaments with reduced adverse effects for the management of acne, psoriasis and other skin diseases.

SUMMARY OF THE INVENTION

[0005] In general, the present invention provides topical compositions and methods for treating skin diseases such as acne and psoriasis.

[0006] In one aspect, this invention provides a topical pharmaceutical composition for treating skin diseases, including acne and psoriasis, comprising: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0007] In another aspect, this invention provides a method of treating skin diseases, including acne and psoriasis, comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from the skin disease, wherein the composition comprises: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

[0008] According to other aspects, the topical pharmaceutical composition may comprise tazarotene or the salt thereof at 0.01 to 0.049 percent by weight of the composition, or at about 0.045 percent by weight of the composition.

[0009] According to another aspect, the tazarotene or tazarotenic acid salt may be dissolved in a liquid oil component of the emulsion.

[0010] According to another aspect, the topical pharmaceutical composition may contain the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.

[0011] According to various aspects, the oil phase of the emulsion may comprise a liquid oil component comprising a DCAE, a MCAE, or combinations thereof. In other aspects, the oil phase includes diethyl sebacate as the DCAE.

[0012] According to other aspects, the aqueous phase of the emulsion may comprise water and a carbomer homopolymer.

[0013] According to another aspect, the topical pharmaceutical composition may comprise: an aqueous phase comprising water, a carbomer homopolymer, and a polymeric emulsifier; an oil phase comprising at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil, and the tazarotene or the tazarotenic acid salt. According to other aspects, the aqueous phase may further comprise a humectant or a preservative, such as at least one member selected from the group consisting of methylparaben, propylparaben and sorbitol.

[0014] According to other aspects, the topical pharmaceutical composition may have the form of a lotion, or of a cream.

[0015] According to another aspect, the topical pharmaceutical composition may have a pH of about 4 to about 6.

[0016] For the methods of this invention, the step of applying may be carried out once per day for at least eight weeks. According to one aspect, the applying is carried out once per day for at least twelve weeks.

[0017] According to other aspects, the composition may be applied to an affected area of a body of a subject suffering from acne vulgaris in order to treat that condition.

[0018] Other features and advantages of the present invention will become apparent from the accompanying drawings and the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

[0019] Figure 1 is a graph of EGSS by visit.

[0020] Figure 2 is a graph of change in inflammatory lesions from baseline.

[0021] Figure 3 is a graph of change in non-inflammatory lesions from baseline.

[0022] Figure 4 are graphs of cutaneous tolerability.

[0023] Figure 5 includes graphs of cutaneous safety.

DETAILED DESCRIPTION OF THE INVENTION

[0024] In general, the present invention provides topical compositions and methods for treating skin diseases, including acne and psoriasis.

[0025] Throughout this disclosure, unless otherwise indicated, the concentration of an ingredient of the composition is in percent by weight of the total composition.

[0026] In one aspect, the topical pharmaceutical composition comprises tazarotene, or a pharmaceutically acceptable salt of tazarotenic acid, at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or the tazarotenic acid salt is included in a composition at a positive concentration less than 0.05 wt%.

[0027] In certain embodiments of the present invention, tazarotene or the tazarotenic acid salt is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition ("wt%"). For example, this component is present in the range from about 0.01 to about 0.049 wt%, or from about 0.01 to about 0.045 wt%, or from about 0.02 to about 0.045 wt%, or from about 0.03 to about 0.045 wt%, or at about 0.045 wt%. Specific concentrations of this component may be 0.01 wt%, 0.015 wt%, 0.02 wt%, 0.025 wt%, 0.03 wt%, 0.035 wt%, 0.04 wt%, and 0.045 wt%.

[0028] In one aspect, the topical pharmaceutical composition comprises an oil-in-water emulsion as a carrier vehicle, in which an internal oil phase is dispersed in a continuous aqueous phase. The emulsion may be a macroemulsion, a

microemulsion, or a nanoemulsion. The composition may have the dosage form of gel, lotion, or cream, or ointment, or liquid, or oil, or spray or foam.

[0029] In addition to the tazarotene active ingredient, the composition of the present invention may comprise one or more dermatologically acceptable excipients, such as liquid oils, waxes viscosity-modifying agents, thickening agents, gelling agents, alcohols, surfactants, chelating agents, buffers, preservatives, humectants, emollients, stabilizers, diluents, dispersing agents, emulsifiers, wetting agents, stabilizers, pH adjusters, solvents or cosolvents.

[0030] The composition of the invention may desirably contain a thickening agent to provide viscosity so that the formulation may be provided in the form of a gel, lotion, cream, or ointment. The thickening agent may be miscible or soluble in an aqueous fluid. Non-limiting examples of suitable thickening agents include acacia, alginic acid and its salts, hyaluronic acid and its salts, carbomers (also known as carboxy vinyl polymers, which are cross-linked polyacrylic acid), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohol, tragacanth, xanthan gum, magnesium aluminum silicate, and bentonite. The thickening agent may also reside in the oil or lipophilic portion of the formulation. Examples of suitable lipophilic thickening agents include cetyl alcohol, stearyl alcohol, glyceryl stearate, white beeswax, microcrystalline wax, hydrogenated polyisobutane polymers, and emulsifying wax.

[0031] A suitable group of thickening agents is carbomers, such as Carbopol® and polycarbophil (The Lubrizol Corporation, Wickliffe, Ohio). Carbopol® homopolymers are polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol. Carbopol® copolymers are polymers of acrylic acid and C₁₀-C₃₀ alkyl acrylate crosslinked with allylpentaerythritol. Carbopol® interpolymers are carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester. Noveon® polycarbophil is a polymer of acrylic acid crosslinked with divinyl glycol.

[0032] A surfactant or emulsifier is optionally included, if desired or required. Pharmaceutically acceptable anionic, cationic, or non-ionic surfactants may be included in a composition of the present invention. Non-ionic surfactants are preferred. Non-limiting examples of non-ionic surfactants are Octoxynol (also known as Macrogol tetramethylbutylphenyl ether, octylphenoxy polyethoxyethanol, or polyoxyethylene octylphenyl ether), such as Octoxynol 1, 3, 5, 8, 9, 10, 12, 13, 16, 30, 40, 70 (wherein the number indicates the number of repeating oxyethylene units), or other Octoxynols that comprise different numbers of repeating units of oxyethylene in the side chain, sorbitan esters (such as sorbitan monooleate and sorbitan monostearate, commonly known by their trade names Span 80 and Span 60), polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade

names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc.), other nonionic surfactants such as Brij® (polyoxyethylene alkyl ether having a formula of $\text{CH}_3-(\text{CH}_2)_{10-18}-(\text{O}-\text{C}_2\text{H}_4)_{1-25}-\text{OH}$), Myrj® (stearic acid esterified with polyoxyethylene having 40-100 repeating oxyethylene units), and long chain fatty alcohols (e.g., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosahexaenoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms).

[0033] In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used. These are polymers of acrylic acid, modified by long chain (C₁₀-C₃₀) alkyl acrylates, and crosslinked with allylpentaerythritol.

[0034] An anionic emulsifier may be used, such as sodium or potassium oleate, triethanolamine stearate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Still other emulsifiers include glyceryl monostearate, polyoxyethylene monooleate, polyoxyethylene monostearate, polyoxyethylene monolaurate, potassium oleate, sodium lauryl sulfate, sodium oleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, triethanolamine oleate, polyoxyethylene

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sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monooleate, and polyoxyethylene sorbitan trioleate.

[0035] The formulation desirably contains a dermatologically acceptable humectant such as glycerin, sorbitol, hexylene glycol, propylene glycol, or urea. In addition, the formulation may contain an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. Chelating agents such as EDTA and citric acid and their salts may be included in a formulation of the present invention.

[0036] The liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature. For example, in one embodiment, the liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature of 22 °C. The liquid oil component may be selected from one or more ingredients from the group consisting of dicarboxylic acid esters ("DCAE"), monocarboxylic acid esters ("MCAE"), fish-liver oil, long-chain triglycerides (wherein each side chain has 14-18 carbons, such as peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, olive oil, cotton seed oil, or derivatives thereof), propylene glycol diesters, medium-chain triglycerides (such as those wherein each side chains has 8-10 carbons; e.g., capric/caprylic acid triglycerides), hydrocarbons like mineral oil, light mineral oil, squalene, and

squalane, fatty alcohols (such as octyldodecanol and isostearyl alcohol), and fatty acids (such as isostearic acid and oleic acid).

[0037] In some embodiments, the liquid oil component comprises a dicarboxylic acid ester and light mineral oil. In some other embodiments, the liquid oil component comprises one or more long-chain triglycerides.

[0038] The formulation may include other lipophilic liquids in an amount that is sufficient to be miscible with the dicarboxylic acid ester and/or monocarboxylic acid ester. The lipophilic liquid may be an emollient such as lanolin oil, mineral oil, light mineral oil, isostearic acid, squalene, octyldodecanol, fractionated coconut oil, cyclomethicone, or dimethicone.

[0039] In addition to the liquid oil component, the formulation may contain water insoluble or practically insoluble ingredients that are not liquid at room temperature, but are soluble in the liquid oil component.

[0040] A DCAE that is suitable for the present invention has the formula $R_1OOC-(CH_2)_n-COOR_2$, wherein R_1 and R_2 are alkyl groups containing between 1 and 4 carbons or aryl groups and may be the same or may be different and wherein $(CH_2)_n$ is a straight or branched chain and n is between 1 and 12. Examples of DCAEs containing one or more aryl groups are dibenzyl esters of dicarboxylic acids. A preferred dicarboxylic acid ester is diethyl sebacate, which has the formula $CH_3CH_2OOC-(CH_2)_8-COOCH_2CH_3$. Examples of other suitable dicarboxylic acid esters (where R_1 and R_2 are the same) are dimethyl, diethyl, dipropyl, diisopropyl,

dibutyl and diisobutyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, and azalate. Examples of suitable dicarboxylic acid esters (where R_1 is different from R_2) are methyl ethyl, methyl propyl, methyl butyl, methyl isopropyl, ethyl propyl, ethyl butyl, ethyl isopropyl, and propyl butyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, azalate, and sebacate.

[0041] In some aspects, diethyl sebacate is included at 0.1 to 20 wt%, or at 0.5 to 10 wt%, or at 2 to 4 wt% of the weight of the composition.

[0042] Alternatively, or in combination with the DCAE, the formulation may contain a MCAE. The MCAE that is suitable for the present invention has the formula $\text{CH}_3-(\text{CH}_2)_n-\text{COOR}_1$, wherein R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and wherein $(\text{CH}_2)_n$ is straight or branched chain and n is between 1 and 12. Examples of such monocarboxylic acid esters include methyl, ethyl, propyl, isopropyl, butyl, or an aryl such as benzyl formate, acetate, propionate, butyrate, valerate, laurate, myristate, palmitate, and stearate. Examples of preferred monocarboxylic acid esters are isopropyl palmitate and isopropyl myristate.

[0043] The liquid oil phase may beneficially be used to dissolve one or more of the active ingredients within the emulsion. In one embodiment the tazarotene component is dissolved in the liquid oil phase within the formulation at room temperature. In another embodiment the tazarotene component is suspended within the formulation at room temperature. In the case wherein the tazarotene component

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is suspended in the formulation, this suspended active ingredient may be micronized, namely that the mean particle size is preferably about 25 microns in diameter or less.

[0044] In one aspect, a composition of the present invention comprises the ingredients at the concentrations shown in Table 1.

Table 1

Compositions of the Present Invention for Treating Skin Diseases

Ingredient	Concentration (wt%)		
	Range 1	Range 2	Range 3
Tazarotene or Tazarotenic Acid Compound	0.01-0.049	0.02-0.045	0.03-0.045
Emollient, Solvent, and/or Thickener	0.5-40	1-25	2-20
Emulsifier	0.25-10	0.5-7	1-5
Humectant	0-15	2-12	3-10
Polymeric Thickener	0.05-2	0.1-1.5	0.3-1
Pharmaceutical Aids	q.s.	q.s.	q.s.
Purified water	q.s. to 100	q.s. to 100	q.s. to 100

[0045] Non-limiting examples of compositions of the present invention are shown in Table 2.

Table 2

Some Emulsion Compositions of the Present Invention for Treating Acne

Ingredient	Function	Concentration (wt%)			
		Range 1	Range 2	Range 3	Composition A
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Note: ⁽¹⁾ These ingredients are broadly classified as Pharmaceutical Aids.

[0046] A lotion having a composition as shown Composition A of Table 2 may be prepared as follows.

[0047] A separate aqueous phase is made. In a manufacturing vessel equipped with a mixing implement (such as a propeller) and temperature control, purified

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water and disodium edetate dihydrate are combined and the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and heated to approximately 75 °C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40 °C with continued mixing. With continuous mixing, Carbopol® 981 and Pemulen™ TR-1 carbomers are added to the mixture and dispersed. Mixing continues until the two carbomers are fully dispersed and hydrated.

[0048] A separate oil phase is made. In a vessel equipped with a mixing implement such as a propeller, diethyl sebacate, and tazarotene are combined. The mixture is agitated until a solution is achieved. With continuous mixing, light mineral oil and sorbitan monooleate are added. Mixing is continued until a solution is obtained.

[0049] In a separate vessel, an approximate 2.5 N solution of sodium hydroxide is prepared.

[0050] With high speed mixing, the oil phase containing the active ingredient (tazarotene) is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Mixing speed is decreased and mixing continued for an additional time of 10 minutes to 1 hour. With continuous mixing, an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5 ± 0.5 . Mixing continues further until a homogeneous lotion is obtained, such as for 30 minutes to 3 hours.

[0051] A first clinical study in acne patients was conducted to compare the efficacy of a composition of the present invention containing tazarotene (the “Composition A” lotion of Table 2).

[0052] A first placebo (“Lotion Placebo”) corresponded to and had a similar viscosity as Composition A but lacked tazarotene. A second placebo (“Cream Placebo”) corresponded to the Lotion Placebo but employed carbomer homopolymer type C in place of carbomer homopolymer type A to yield a higher viscosity emulsion with a viscosity similar to 0.1% tazarotene cream employed in the study. This allows for better blinding of the test formulations and control of the clinical study. In the following results, data for Lotion Placebo and Cream Placebo may be combined and reported as “Combined Placebo”.

[0053] Additionally, commercially available 0.1% tazarotene cream (Tazorac® 0.1% cream) was employed in this clinical study for comparison purposes.

[0054] A double blind, multi-site, randomized clinical study was conducted on patients suffering from acne vulgaris, whereby neither the acne patient nor the investigator knew the identity of the test composition assigned. 210 patients were randomized to receive either Composition A lotion, Tazorac® 0.1% cream, Placebo Lotion and Placebo Cream at a 2:2:1:1 randomization:

69 subjects “Composition A lotion”

72 subjects “Tazorac® 0.1% cream”

34 subjects “Lotion Placebo”

35 subjects “Cream Placebo”.

[0055] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 40, and non-inflammatory lesion count of at least 20 but no more than 100. The blindly labeled lotions were applied to the affected area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0056] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score (EGSS), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0057] Clinical Efficacy was determined primarily based on the percentage of subjects who were treatment successes at 12 weeks. To be judged as a treatment success, as reported in Tables 4, 6, and 7, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to "clear" or "almost clear". Also, the numbers of inflammatory and non-inflammatory lesions were assessed.

[0058] Table 3 reports Baseline Characteristics.

Table 3
Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory lesions

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Inflammatory Lesions			
Mean (SD)	27.2 (5.49)	28.3 (6.0)	27.3 (5.95)
Median	26.0	27.0	26.0
Non-inflammatory Lesions			
Mean (SD)	36.6 (13.17)	37.6 (14.70)	36.6 (13.31)
Median	34.0	34.0	34.0

[0059] Table 4 reports treatment % success on an intention-to-treat (ITT) basis.

Table 4
EGSS (Clear or Almost Clear) by Visit (ITT)

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	0%	0%	0%
Week 4	0%	1.4%	1.4%
Week 8	4.3%	7.2%	5.6%
Week 12	10.1%	18.8%	16.7%

[0060] Table 5 reports absolute change in inflammatory lesions from baseline.

Change in inflammatory and non-inflammatory lesions from baseline is reported in Figures 2 and 3.

Table 5
Inflammatory Lesions by Visit
Absolute Change from Baseline

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
Week 2	-4.7	-2.9	-2.4
Week 4	-7.2	-5.8	-7.8
Week 8	-10.9	-13.2	-12.0
Week 12	-14.0	-18.1	-16.8

[0061] Table 6 reports treatment % success for primary efficacy on an intention-to-treat basis for EGSS at week 12. For EGSS, to be judged as a treatment success, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to “clear” or “almost clear”. For inflammatory and non-inflammatory lesions, absolute change from baseline to week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 6
Treatment % Success (ITT) at 12 Weeks

	Combined Placebo N=69	Composition A N=69	Tazorac® 0.1% Cream N=72
EGSS – Clear or Almost Clear	10.1%	18.8%	16.7%
Inflammatory Lesions Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

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[0062] Table 7 reports treatment % success on a per-protocol basis for EGSS. For lesions, absolute change from baseline to Week 12 in mean inflammatory and non-inflammatory counts is reported.

Table 7
Treatment % Success (PP)

	Combined Placebo N=57	Composition A N=54	Tazorac® 0.1% Cream N=56
EGSS – Clear or Almost Clear	12.3%	20.4%	16.1%
Inflammatory Lesions	-14.2	-18.3	-18.2
Non-inflammatory Lesions	-11.8	-20.8	-21.9

[0063] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by burning, stinging or itching reported by the subjects. This data is summarized in Figure 4. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation and hyper-pigmentations as evaluated by the investigator. This data is summarized in Figure 5.

[0064] Table 8 reports treatment emergent adverse event characteristics.

Table 8
Treatment Emergent Adverse Event Characteristics

	Combined Placebo	Composition A	Tazorac® 0.1% Cream
% Subjects Reporting Any Adverse Event	13.4%	14.7%	26.8%
% Subjects Reporting Any Serious Adverse Event	0%	0%	0%
% Subjects Discontinued Study Due to Adverse Event	0%	0%	1.4%

[0065] Notably, this clinical study showed that Composition A, containing less than half of the tazarotene active ingredient, had a numerically better efficacy than

the Tazorac® 0.1% Cream. Also, the adverse event profile was lower for Composition A than for Tazorac® 0.1% Cream.

[0066] In another aspect, the present invention provides a method for treating acne. The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more times per day for a period of time sufficient to treat such acne. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days. Alternatively, it may be applied two or three times per day for 7-14 days. Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

[0067] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse

events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

[0068] In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene.

[0069] Two larger clinical studies (Studies 301 and 302) in acne patients were conducted to compare the efficacy of a composition of the present invention containing tazarotene (the "Composition A" Lotion of Table 2) to that of a placebo that was the vehicle of Composition A (i.e., without the active ingredient tazarotene).

[0070] These studies were phase-3, multi-center, randomized, double-blind, vehicle-controlled, two-arm, parallel group studies comparing the safety and efficacy of Composition A ("IDP-123 Lotion" or "Composition A Lotion") and IDP-123 vehicle lotion ("Placebo Lotion") in the treatment of acne vulgaris. Neither the acne patient nor the investigator knew the identity of the test composition assigned.

[0071] In the first study (Study 301), 813 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

402 subjects receiving "Composition A Lotion,"

411 subjects receiving "Placebo Lotion."

[0072] In the second study (Study 302), 801 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

397 subjects receiving “Composition A Lotion,”

404 subjects receiving “Placebo Lotion.”

[0073] Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 50, and non-inflammatory lesion count of at least 25 but no more than 100. The blindly labeled lotions were applied to the affected facial area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

[0074] The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator’s Global Severity Score (“EGSS”), and determining the grade of improvement. EGSS included the following grades:

Clear = 0; Almost Clear = 1; Mild = 2; Moderate = 3; Severe = 4.

[0075] Clinical Efficacy was determined primarily based on: (1) superiority in absolute change from baseline to week 12 in mean inflammatory counts; (2) superiority in absolute change from baseline to week 12 in mean non-inflammatory counts; and (3) percentage of subjects who achieve at least a two-grade reduction from baseline and are “Clear” or “Almost Clear” at week 12 in the EGSS.

[0076] Table 9 reports Baseline Characteristics.

Table 9

Subject Baseline Characteristics –
Inflammatory Lesions and Non-inflammatory Lesion Counts

	Study 301		Study 302	
	Composition A Lotion N=402 ⁽¹⁾	Placebo Lotion N=411 ⁽¹⁾	Composition A Lotion N=397 ⁽¹⁾	Placebo Lotion N=404 ⁽¹⁾
Inflammatory Lesions				
Mean (SD)	28.5(7.04)	28.1 (7.04)	28.0 (7.32)	27.9 (7.10)
Median	26.0	26.0	26.0	26.0
Non-inflammatory Lesions				
Mean (SD)	41.1 (15.67)	40.7 (16.29)	41.8 (17.87)	40.6 (16.31)
Median	36.0	34.0	36.0	35.0

[0077] Table 10 reports treatment % success at week 12 on an intention-to-treat (ITT) basis.

Table 10
EGSS (Clear or Almost Clear) at Week 12 (ITT)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Week 12	25.5% (p<0.001)	13.0%	29.6% (p<0.001)	17.3

[0078] Table 11 reports absolute changes in inflammatory and non-inflammatory lesions from baseline at week 12.

Table 11
Inflammatory and Non-Inflammatory Lesions
Absolute Changes from Baseline at Week 12

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
Inflammatory Lesions	-15.6 (p<0.001)	-12.4	-16.7 (p<0.001)	-13.4
Non-inflammatory Lesions	-21.0 (p<0.001)	-16.4	-24.6 (p<0.001)	-16.6

[0079] Table 12 reports assessment of treatment success on a per-protocol basis for EGSS. For lesions, absolute changes from baseline to week 12 in mean inflammatory and non-inflammatory counts are reported.

Table 12
Treatment Success (Per-Protocol Basis)

	Study 301		Study 302	
	Composition A Lotion N=402	Placebo Lotion N=411	Composition A Lotion N=397	Placebo Lotion N=404
EGSS – Clear or Almost Clear	26.8%	14.4%	30.6%	18.3%
Inflammatory Lesions	-15.8	-12.4	-16.4	-13.4
Non-inflammatory Lesions	-21.3	-16.3	-24.1	-15.4

[0080] The compositions were tested for cutaneous safety and tolerability.

Cutaneous tolerability was assessed by itching, burning, or stinging reported by the subjects. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentations, as evaluated by the investigator.

[0081] Table 13 shows the number of subjects reporting moderate or severe itching, burning, or stinging; or being observed to have moderate or severe scaling, erythema, hypopigmentation, or hyperpigmentation. In general, the reported numbers of these conditions are similar between those subjects using Composition A Lotion and Placebo Lotion.

Table 13
Cutaneous Safety and Tolerability

	Study 301		Study 302	
	Composition A Lotion N=387	Placebo Lotion N=392	Composition A Lotion N=392	Placebo Lotion N=399
Scaling				
Moderate	4	2	6	1
Severe	0	0	1	0
Erythema				
Moderate	7	8	13	6
Severe	0	0	1	0
Hypopigmentation				
Moderate	1	1	0	0
Severe	0	0	0	0
Hyperpigmentation				
Moderate	7	9	8	17
Severe	1	2	0	1
Itching				
Moderate	4	2	4	4
Severe	0	0	0	0
Burning				
Moderate	2	0	5	0
Severe	0	0	2	0
Stinging				
Moderate	1	1	3	0
Severe	0	0	1	0

[0082] Table 13 reports treatment emergent adverse event characteristics.

Table 13

Treatment Emergent Adverse Event Characteristics

	Study 301		Study 302	
	Composition A Lotion N=392 ⁽¹⁾	Placebo Lotion N=399 ⁽¹⁾	Composition A Lotion N=387 ⁽¹⁾	Placebo Lotion N=392 ⁽¹⁾
% Subjects Reporting Any Adverse Event	25.5%	19.5%	28.2%	18.6%
% Subjects Reporting Any Serious Adverse Event	0.8%	0.8%	0.3%	0.3%
% Subjects Discontinued Study Due to Adverse Event	3.1%	0.5%	2.6%	0.5%

Note: (1) safety population, which comprises all randomized subjects who were presumed to have used the study drug at least once and who provided at least one post-baseline safety evaluation.

[0083] Notably, these clinical studies showed that the percentages of subjects reporting any serious adverse event for Composition A are no higher than those for the Placebo Lotion, indicating the excellent safety of Composition A.

[0084] The treatment success, as measured by investigator's global assessment of Composition A Lotion (denoted as "EGSS" above) and some commercial products containing a retinoid (as gleaned from their package inserts) is shown in Table 14.

Table 14

Comparison of Treatment Success of Various Products Containing a Retinoid

		Number of Subjects	Treatment Success (%)
Tazarotene Products	Composition A Lotion, 0.045% tazarotene	402	25.5
		397	29.6
	Tazorac Cream, 0.1% tazarotene	218	18
		206	20
	Fabior Foam, 0.1% tazarotene	371	29
		373	28
Tretinoin Products	Altreno Lotion, 0.05% tretinoin	406	16.5
		413	19.8
	Atralin Gel, 0.05% tretinoin	375	21
		299	23
Adapalene Products	Adapalene Gel, 0.3%	258	21
	Adapalene Gel, 0.1%	261	16
	Adapalene Lotion, 0.1%	533	26.3
		535	24.1
	Epiduo Gel, 0.1% adapalene/2.5% benzoyl peroxide	149	21.5
		415	30.1
	0.1% Adapalene in Epiduo vehicle	148	12.2
		420	19.8

[0085] Surprisingly, Composition A Lotion achieved at least similar or higher success rate than other products that contain at least twice the concentration of the active ingredient.

[0086] In another aspect, the present invention provides a method for treating acne vulgaris (acne). The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more (such as 1, 2, 3, or more) times per day for a period of time sufficient to treat such acne vulgaris. For example, such a period of time may be 1 to 30 days or longer as needed. For example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is

applied topically to affected areas of the body once per day for 7-14 days.

Alternatively, it may be applied two or three times per day for 7-14 days.

Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

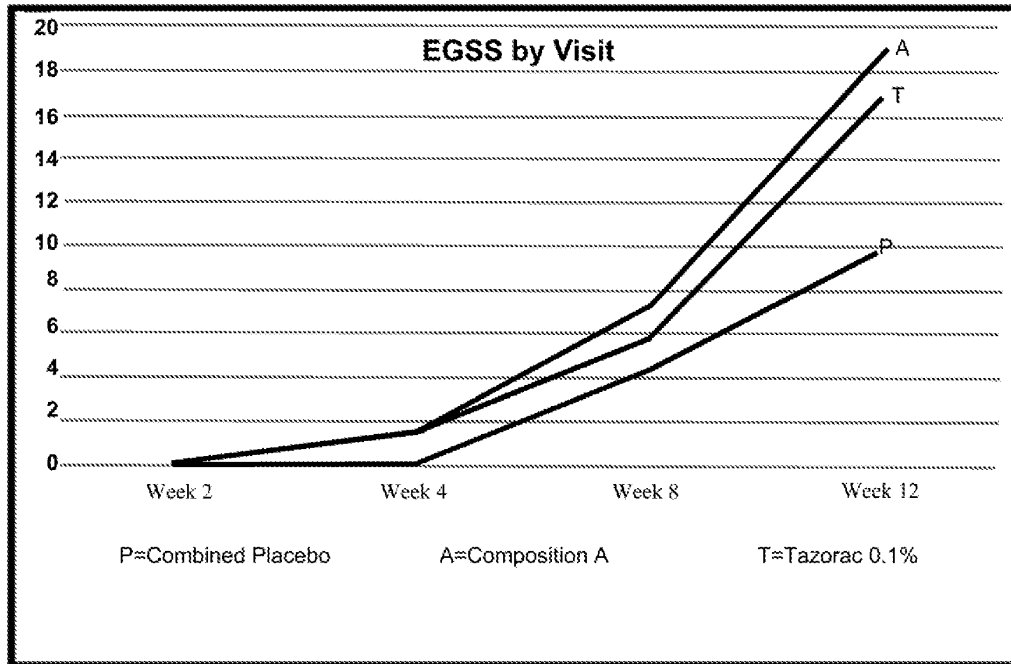
[0087] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

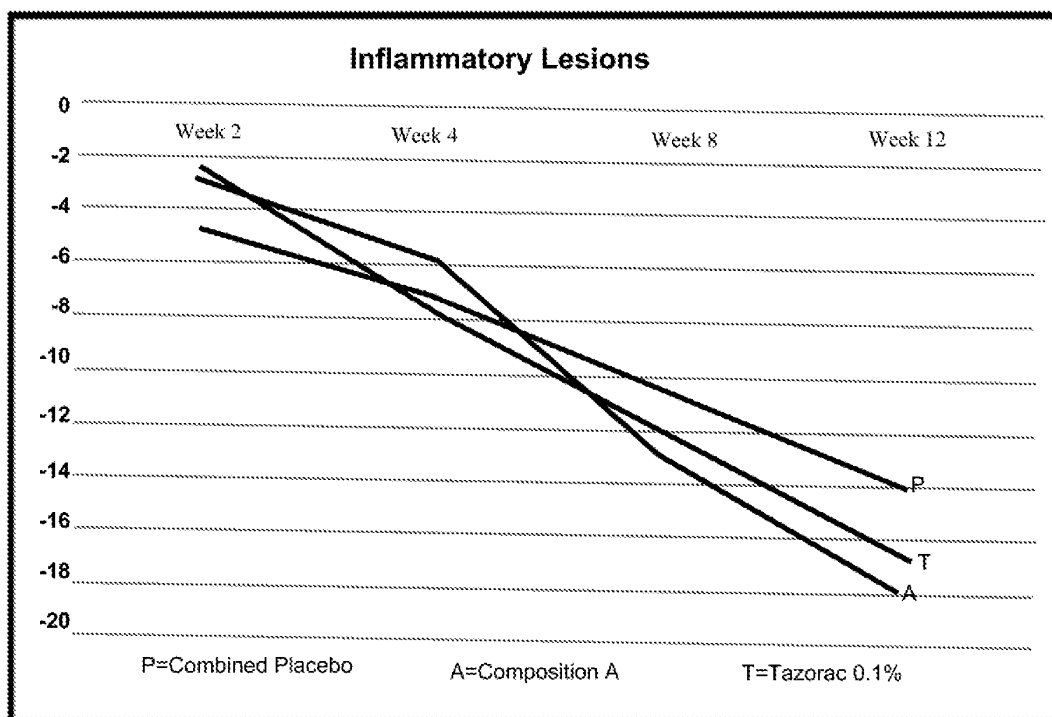
[0088] In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene (Tazorac® Cream).

[0089] While the present disclosure shows and describes a number of exemplary embodiments, it will be manifest to those skilled in the art that various

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further modifications may be made without departing from the spirit and scope of the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

**FIG. 1**

**FIG. 2**

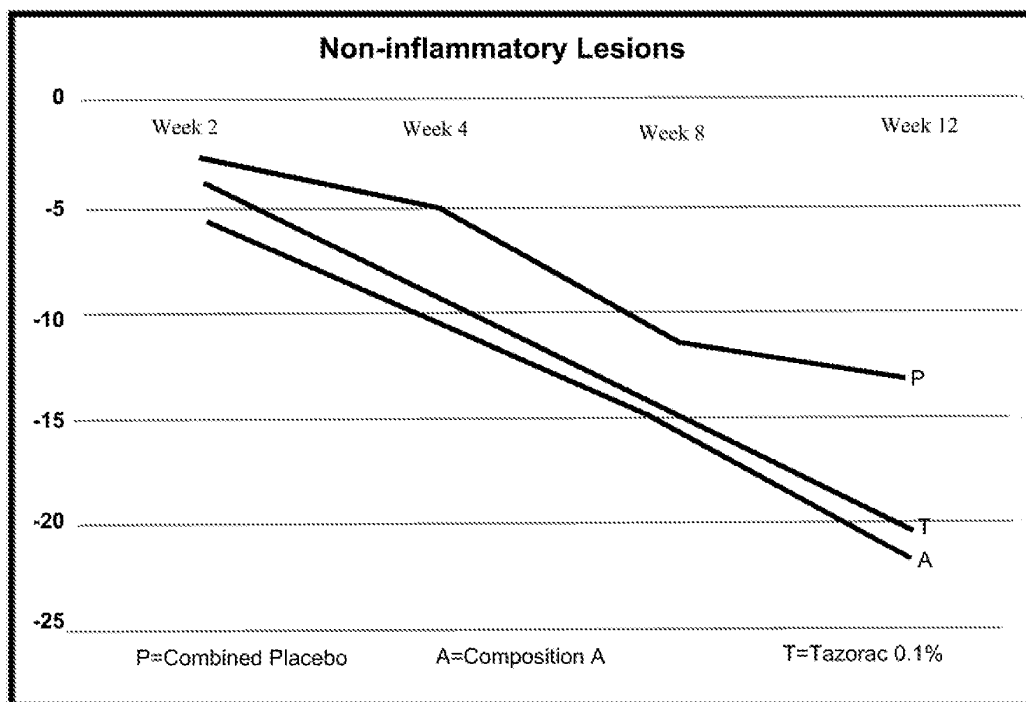
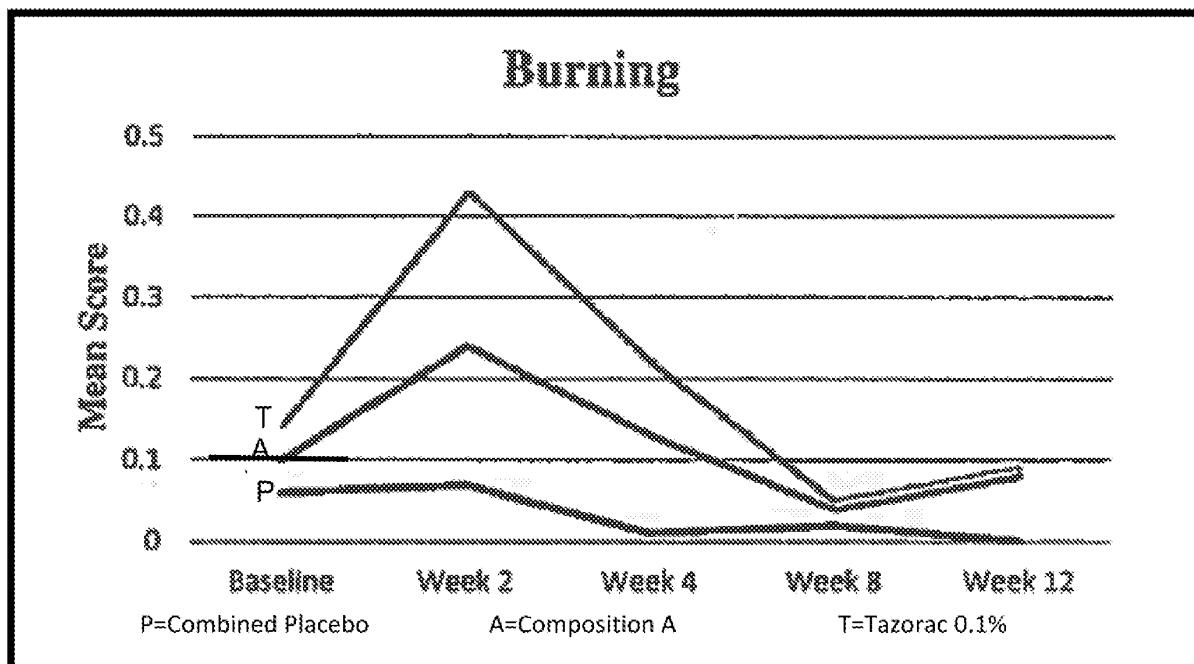
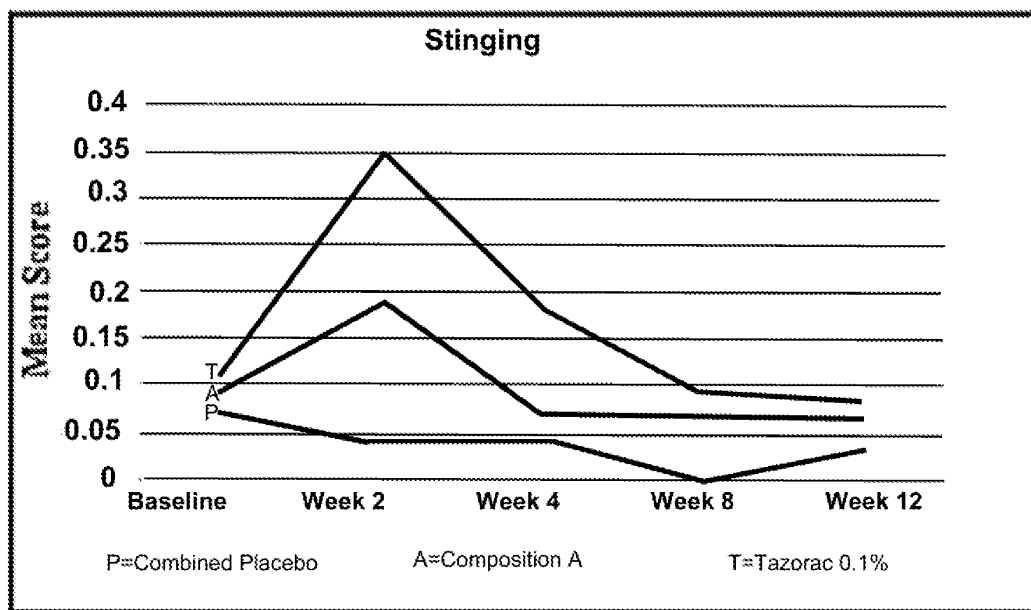
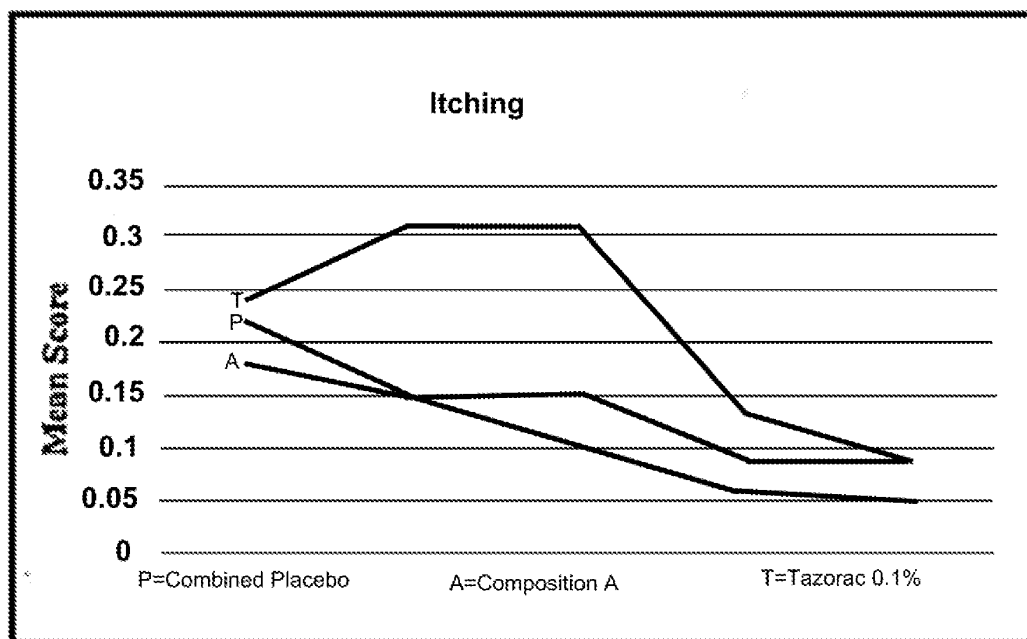
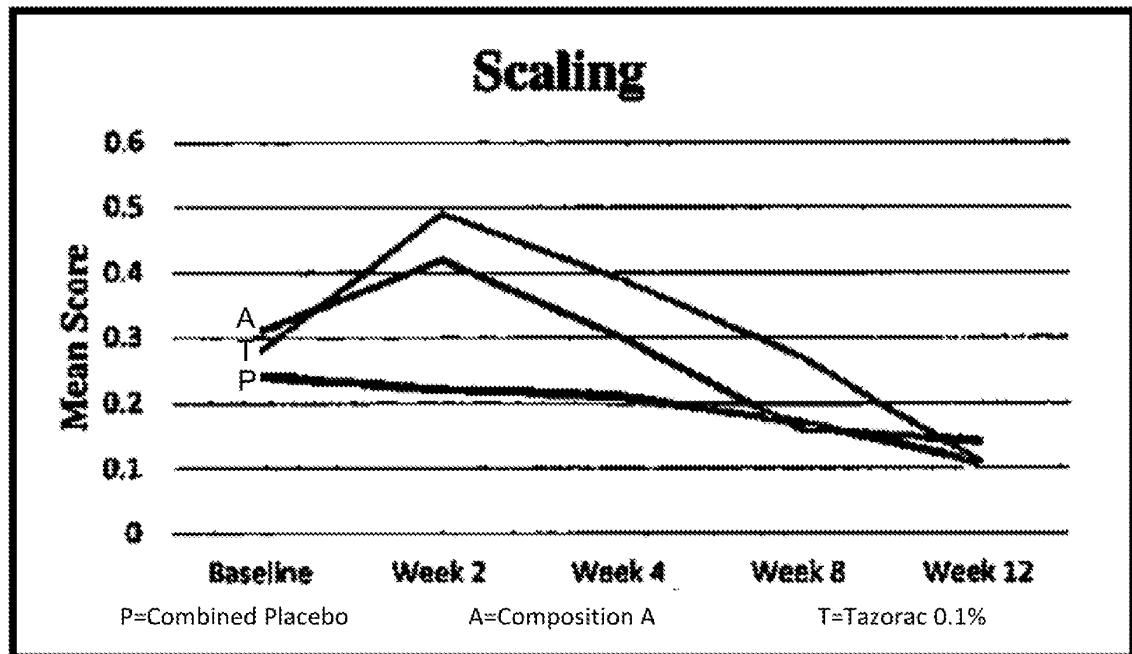


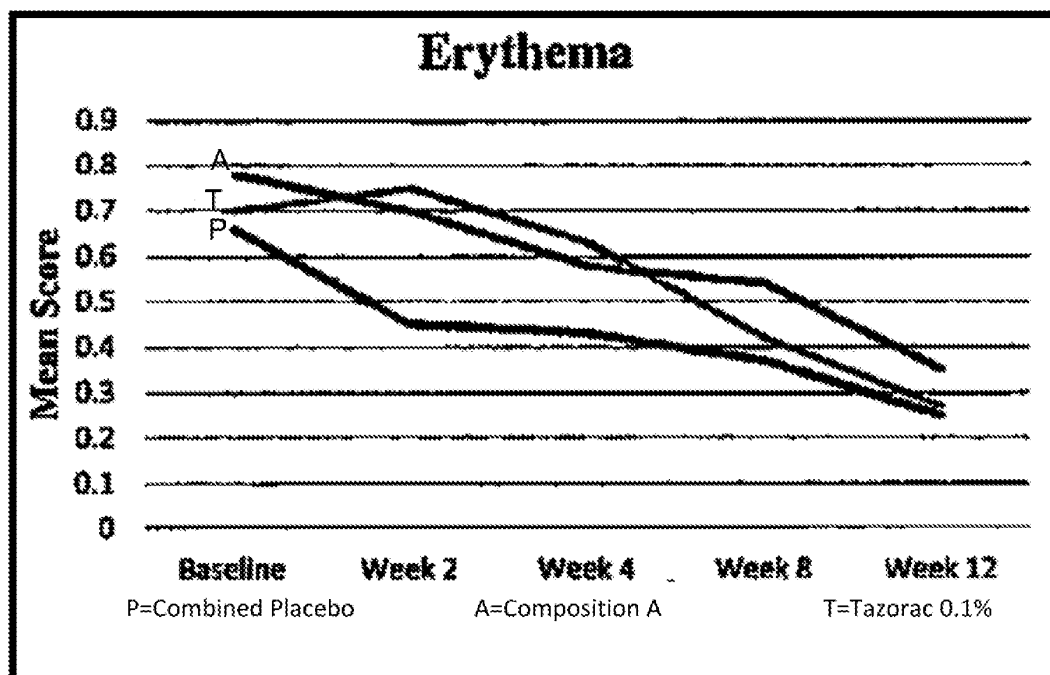
FIG. 3

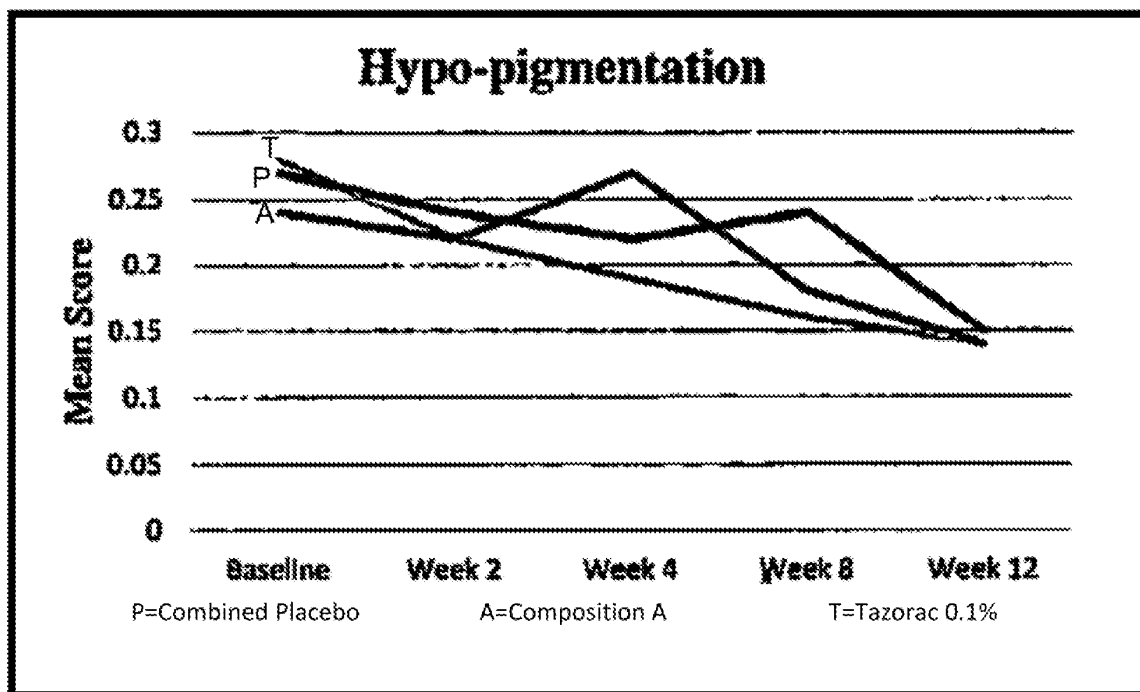
**FIG. 4A**

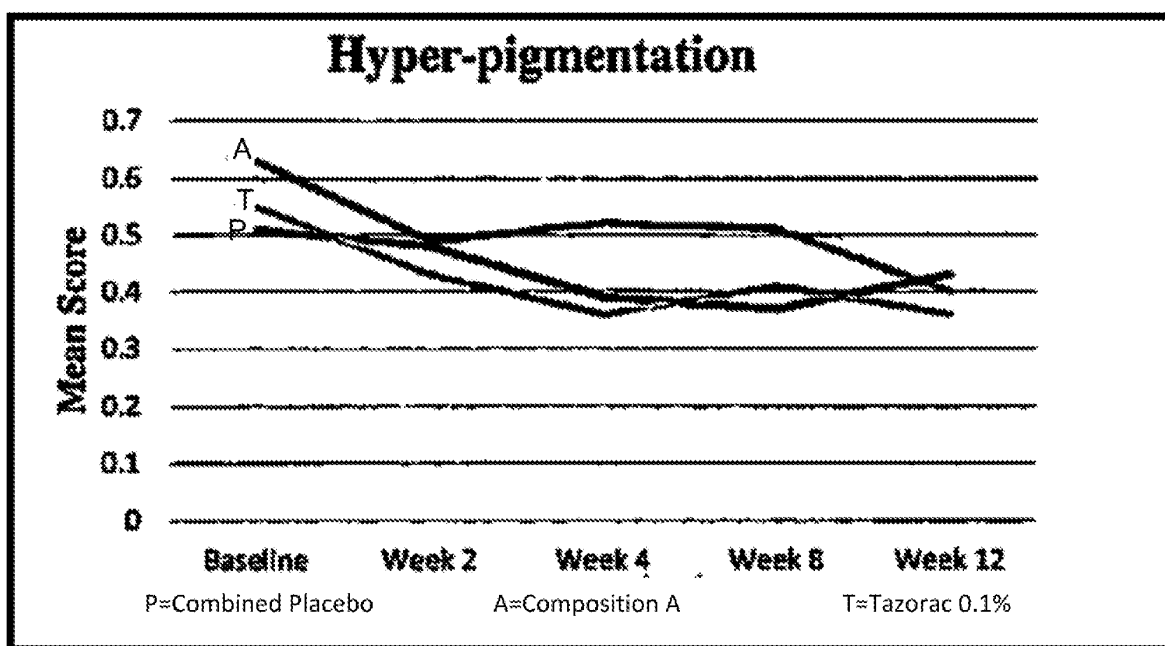
**FIG. 4B**

**FIG. 4C**

**FIG. 5A**

**FIG. 5B**

**FIG. 5C**

**FIG. 5D**

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:		TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES		
First Named Inventor/Applicant Name:		Angel Arturo		
Filer:		Andrew James Anderson/Bethany Weber		
Attorney Docket Number:		99336.000207-CIP		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1720

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First Named Inventor/Applicant Name:	Angel Arturo
Customer Number:	134756
Filer:	Andrew James Anderson/Bethany Weber
Filer Authorized By:	Andrew James Anderson
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	99336-207-CIP_ADS.pdf	1407921	no	9
			592d8d05c8b4d32cd181dc0fccb5ea68a99cac		
Warnings:					
Information:					
2		99336-207-CIP_Spec.pdf	198999	yes	35
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	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Abstract		35	35	
	Claims		31	34	
	Specification		1	30	
Warnings:					
Information:					
3	Drawings-only black and white line drawings	99336-207-CIP_Figures.pdf	2273353	no	10
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4	Fee Worksheet (SB06)	fee-info.pdf	35200	no	2
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New International Application Filed with the USPTO as a Receiving Office

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