not apply. Applicant submits that claim 1 is not indefinite for this reason and respectfully requests that the rejection be withdrawn.

III. Rejection of Claims under 35 U.S.C. § 103

Claims 1, 6-10, 12, and 27-28 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Tazorac ("Highlights of Prescribing Information, LABEL (fda.gov), December 2013) in view of Angel *et al.* (WO 2012/087443; "Angel"). To the extent that the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The allegations in the pending office action are similar to those made previously. For example, the Examiner alleges that:

> It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl, propyl paraben water, carbopol® and Pemulen™ to the oil-in-water with an oil phase an aqueous phase in a cream of tazarotene of Tazorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben and purified water q.s. ad because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl, propyl paraben, water and Pemulen™ are useful in topical administration for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.[1]

Applicant respectfully disagrees. As previously explained, one of skill in the art would *not* be motivated to combine the references as suggested in the Office Action and one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed composition.

A. ONE OF SKILL IN THE ART WOULD NOT BE MOTIVATED TO COMBINE THE CITED REFERENCES.

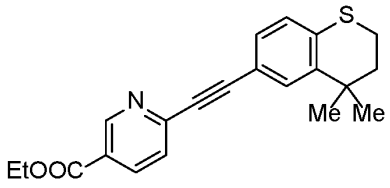
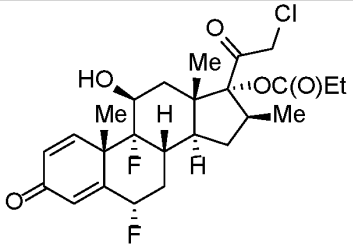
As noted above, it is alleged that the skilled artisan would be motivated to modify the cream of Tazorac by using diethyl sebacate, sorbitol, and parabens, because Angel discloses that such excipients are useful for enhancing solubility, chemical stability, and penetration properties. Applicant respectfully submits that the skilled artisan would *not* be motivated to combine the

[1] Office Action at pages 10-11.

references as proposed in the Office Action, because the references are directed to two very different active agents.

In the most recent Office Action, the Examiner repeatedly states that the claimed formulation would be obvious "absent evidence to the contrary." According to MPEP § 2145, ***Office personnel should consider all rebuttal arguments and evidence presented by applicants***, Applicant respectfully seeks to confirm that the Examiner has considered the evidence in the form of the previously-submitted chemical information and accompanying Declaration of Dr. Gordon Jay Dow submitted on May 27, 2021 under 37 C.F.R § 1.132 ("the Declaration").

Dr. Dow, who is named as a co-inventor on the Angel reference, is an expert in the field of formulation development for topical treatment of skin conditions. In the Declaration, Dr. Dow explained that the skilled artisan would *not* be motivated by the disclosure of Angel to modify Tazorac so as to arrive at the claimed lotion composition. Dr. Dow explained that halobetasol propionate, a corticosteroid disclosed by Angel for the treatment of psoriasis, has a *vastly different* chemical structure and physicochemical properties as compared to tazarotene, a retinoid, disclosed by Tazorac. Some of these differences are tabulated below. As shown below, the logP values for tazarotene, a retinoid, and halobetasol propionate, a steroid, indicate that tazarotene is almost 1000 times less lipophilic than halobetasol propionate.

	Tazarotene	**Halobetasol propionate**
		
Mol. Wt.	351.46	484.96
logP [a]	5.987+/-0.448	2.947+/-0.630

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 at 25 °C.

Dr. Dow explained that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This is because the physicochemical properties of halobetasol propionate, a steroid, are entirely different from the physicochemical properties of tazarotene, a retinoid. Dr. Dow explained that the skilled artisan

would *not* expect Angel's results for halobetasol propionate to extend to a tazarotene formulation given the considerable differences between the active agents. Rather, the skilled formulator would understand that the stability and delivery considerations for halobetasol propionate could *not* be translated to tazarotene, and the skilled formulator would *not* look to the disclosure of Angel when formulating tazarotene.

Applicant respectfully submits that the physical differences between the two active agents, as explained in the Declaration, are indeed the "evidence to the contrary" that the Examiner repeatedly calls for. For at least this reason, Applicant respectfully maintains that one of skill in the art would not be motivated to combine the references.

B. THE SURPRISING PROPERTIES OF THE CLAIMED COMPOSITION ARE EVIDENCE OF NON-OBVIOUSNESS.

It is made clear in the MPEP that "A chemical composition and its properties are inseparable."[2] The improved efficacy and tolerability of the claimed lotion composition, as compared to TAZORAC cream, result from the components of the lotion as presently claimed. Dr. Dow previously explained that he and other skilled artisans would not have expected these improved properties based on the teachings of Tazorac and Angel.

The increased efficacy provided by the claimed 0.045% tazarotene lotion, as compared to TAZORAC cream, is set forth in Table 6. Regarding this data, the Examiner alleged the following:

> (I)n looking at table 6 in which applicants assert unexpected results; applicants compare 0.1% to composition A, which is 0.45%. The difference appears to approximately 1.3% favoring the 0.45% which is additive effect rather than synergism or unexpected results.[3]

Applicant respectfully disagrees. Table 6 is reproduced below, and shows that the improvement over placebo observed for 0.045% tazarotene lotion ("Composition A") was substantially higher than the improvement over placebo observed for 0.1% TAZORAC cream.

[2] MPEP § 2112.01(II)
[3] Office Action at page 4.

Table 6
Treatment % Success (Intention-To-Treat) 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%

Applicant notes that 18.8% of acne patients receiving Composition A reached an Evaluator's Global Severity Score (EGSS) equating to "clear" or "almost clear," whereas only 16.7% of patients receiving TAZORAC cream achieved this score. Applicant notes that this difference amounts to a **31.8% improvement** for Composition A, as compared to TAZORAC, over the combined placebo population in the study as outlined below.

Improvement over placebo: $\frac{(Composition\ A\ result - placebo\ result) - (TAZORAC\ result - placebo\ result)}{(TAZORAC\ result - placebo\ result)} \times 100\%$

$\frac{(18.8\% - 10.1\%) - (16.7\% - 10.1\%)}{(16.7\% - 10.1\%)} \times 100\%$

$= 31.8\%$

The *greater* efficacy over placebo provided by Composition A in the claimed method is particularly surprising when considering that the method employed *less than half* the tazarotene dose of TAZORAC. Applicant submits that the skilled artisan would *not* expect to increase the efficacy when decreasing the amount the active agent by over half. On the contrary, one of skill in the art would expect that decreasing the amount of tazarotene would decrease the efficacy of the method. Nothing in the cited references suggests otherwise. Indeed, nothing in the cited references suggests the superior results provided by administering the claimed amount of tazarotene using the claimed vehicle in the claimed method.

Applicant respectfully reiterates that one of skill in the art would *not* be motivated to combine the references as suggested in the Office Action due to the vast differences in the chemical structures and physicochemical properties of the active agents. Even if the

combination were made in the absence of such motivation, one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed lotion. For at least these reasons, Applicant submits that the claims are *not* obvious over the cited references and respectfully requests that the rejection be withdrawn.

IV. Double Patenting Rejections

The claims are rejected on the grounds of non-statutory obviousness-type double patenting over claims in U.S. Patent Nos. 10,426,787 and 10,251,895, as well as over claims in Pat. Appl. No. 16/179,561 (now issued as U.S. Pat. No. 11,311,482).

The Examiner has not yet indicated that the pending claims are in condition for allowance. As such, the filing of a terminal disclaimer is premature. Applicant therefore respectfully requests, without acquiescing to the validity of these rejections, that the rejections be held in abeyance until the pending claims are in condition for allowance. At that time, Applicants will address the non-statutory double patenting rejections as necessary.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (925) 472-5000.

Respectfully submitted,

/Eugenia Garrett-Wackowski/
Eugenia Garrett-Wackowski
Registration No. 37,330

KILPATRICK TOWNSEND & STOCKTON LLP

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/13/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LINDA HUMES/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

PTO/AIA/31 (03-14)
Approved for use through 11/30/2020. OMB 0651-0031
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NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional): 095920-004120US-1240999

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, on Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on December 13, 2021.

Signature /Sharleen Lane/

Typed or printed name Sharleen Lane

In re Application of: Arturo Angel

Application Number	Filed
16179576	2018-11-02

For: TOPICAL COMPOSITIONS AND METHODS FOR TR

Art Unit	Examiner
1627	Kathrien Cruz

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 840

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 20-1430.

☑ Payment made via EFS-Web.

☑ A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed.
For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant

☑ attorney or agent of record Registration number 69,844

☐ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Andrew Presley/

Typed or printed name Andrew D. Presley

Telephone Number (415) 273-4310

Date December 13, 2021

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 41.20(b)(1) and 41.31. 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 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application 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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IPR Petition - USP 11,311,482

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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 inspection 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.

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IPR Petition - USP 11,311,482

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:	Arturo Angel
Filer:	Andrew David Presley/Sharleen Lane
Attorney Docket Number:	095920-004120US-1240999

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:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
NOTICE OF APPEAL	1401	1	840	840
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
		Total in USD ($)		**2320**

Electronic Acknowledgement Receipt	
EFS ID:	44502247
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:	Arturo Angel
Customer Number:	112120
Filer:	Andrew David Presley/Sharleen Lane
Filer Authorized By:	Andrew David Presley
Attorney Docket Number:	095920-004120US-1240999
Receipt Date:	13-DEC-2021
Filing Date:	02-NOV-2018
Time Stamp:	16:46:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2320
RAM confirmation Number	E2021BCG46463658
Deposit Account	
Authorized User	
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	095920-004120US_EOT.pdf	177487 5e7108bbc16af58c0fe48e19f9373b2500d5aa5a	no	1
Warnings:					
Information:					
2	Notice of Appeal Filed	095920-004120US_NOAP.pdf	1420331 566aa061dc7deeff7256c2af47e79245ed652734	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	40461 d2eed702376421dc3dca1dc5ebf561cb8a86780c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1638279		

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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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

PTO/AIA/22 (10-20)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 095920-004120US-1240999
Application Number 16/179,576	Filed November 2, 2018
For TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES	
Art Unit 1627	Examiner Kathrien Ann Cruz

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$_____
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$_____
☒ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$1,480
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$_____
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$_____

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 69,844

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____

/Andrew Presley/	December 13, 2021
Signature	Date
Andrew D. Presley	(415) 273-4310
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application 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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Arturo Angel	095920-004120US-1240999	1093

112120 7590 06/11/2021

Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/11/2021	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):

KTSDocketing2@kilpatrick.foundationip.com
ipefiling@kilpatricktownsend.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 16/179,576	Applicant(s) Angel et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5/27/2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,6-10,12 and 27-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,6-10,12 and 27-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 5/27/2021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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, 6-10, 12 and 27-28 is pending.

Applicants response filed 5/27/2021 has been received and entered in the application.

Action Summary

Claims 1, 6-10, 12 and 27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record is maintained with modification due to applicants amendment of claims.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787 is maintained with modification due to applicant's amendment of claims.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895 is maintained with modification due to applicant's amendment of claims.

Claims 1, 6-10, 12 and 27-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending

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Application No. 16/179,561 is maintained with modification due to applicant's amendment of claims.

Response to Arguments

Applicants argue that Dr. Dow explains that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This argument has been fully considered but has not been found persuasive the formulation for delivery as applicants assert is the very same formulation as instant claimed. Therefore, it would have been obvious to substitute tazarotene in same formulation. Additionally, Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate. it would have been obvious to substitute tazarotene instead of halobetasol propionate because both agents are known in the art to treat skin disorder and the composition for delivery (as applicants assert) is the same, thus taken the cited art, it would have been obvious to administer tazarotene with diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary

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Applicants assert unexpected results (e.g. surprising properties) in which Dr. Dow that a skilled artisan would not expect the surprising advantages of the claimed lotion composition. This argument has been fully considered but has not been found persuasive. Tazaorac specifically discloses 0.5%. Additionally, in looking at table 6 in which applicants assert unexpected results; applicants compare 0.1% to composition A, which is 0.45%. The difference appears to approximately 1.3% favoring the 0.45% which is additive effect rather than synergism or unexpected results. Furthermore, Tazaorac specifically discloses tazarotene in a concentration of 0.05%, which is half (50%) the dose of the comparison of 1%. Therefore, it would have been obvious to optimize said composition to 0.045% from a dose of 0.05% as disclosed by Tazaorac with a reasonable expectation of success absence evidence to the contrary.

Applicants argue that there is has not been a prima case of obviousness established by the Office. This argument has been fully considered but has not been found persuasive. Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of

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water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

Applicants again argue that Angel is drawn to a corticosteroid composition whereas the instant claims are drawn to tazarotene composition. This argument has been fully considered but has not been found persuasive. Tazaorac teaches

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(tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ

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diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary. Additionally, it would have been obvious to substitute tazarotene instead of halobetasol propionate because both agents are known in the art to treat skin disorder and the composition for delivery (as applicants assert) is the same, thus taken the cited art, it would have been obvious to administer tazarotene with diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary

Previous Rejection with modifications due to applicant's amendment of claims.

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.

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Claims 1, 6-10, 12 and 27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record.

Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). (11, under Description).

Tazaorac does not disclose diethyl sebacate, sorbitol solution, methyl and propyl paraben nor the concentrations of the inactive agents. Tazaorac does not disclose the pH.

Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the agent in a formulation containing a liquid oil component that includes a dicarboxylic acid ester and/or a monocarboxylic acid ester (page 6). Angel teaches the components of the aqueous

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phase and of the oil phase may be separately combined and mixed until homogenous solutions are obtained and then the aqueous solution and the oil solution may be combined and mixed, such as by shear mixing, to form the formulation. The oil phase may be added to the water phase, or the water phase may be added to the oil phase. The phases may be combined and mixed, such as at elevated temperatures of 50-90°C or at room temperature, that is between 20-30°C, or at a temperature between room temperature and the elevated temperatures (page 12). Angel teaches that with high speed rotor-stator mixing, the oil phase containing the drug is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Anger teaches that the thickening agent is miscible or soluble in an aqueous fluid. Examples of suitable thickening agents include acacia, alginic acid, bentonite, carbomers, also known as carboxy vinyl polymers, such as sold under the tradename Carbopol® (page 10 bridging page 11). Angel further teaches that in a manufacturing vessel, purified water and disodium edetate dihydrate are combined a d 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 is 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 propeller agitation Carbopol 981 at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% are added to the mixture and fully dispersed. (page 20). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 %

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(example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0 (table 4). Angel exemplify a 0.01 %wt. a formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate and purified water, q.s ad (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl, propyl paraben, water, carbopol® and Pemulen ™ to the oil-in-water with an oil phase and aqueous phase in a cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben and purified water q.s. ad because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl, propyl paraben, water and Pemulen ™ are useful in topical administration for enhancing the solubility, chemical stability and

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penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating a skin disorder consisting of tazarotene would have found it prima facie obvious to administer the concentration of tazarotene in the emulsion of Tazaorac in order to arrive at the instantly claimed emulsion. Tazaorac teaches the concentration of tazaotene of 0.05% and 0.1% contains 0.5 and 1 mg respectively. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been

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motivated to optimize the workable ranges disclosed by Tazaorac, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazaorac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to the of concentrations of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, is diethyl sebacate in a concentration of 2.10 % (the combination of mineral oil and diethyl sebacate is 11.8%), sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Carbopol® at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% as disclosed by Angel. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d

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1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the workable ranges disclosed by Tazaorac and Angel, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Pemulen™ (polymeric emulsifier) at a concentration of 0.4% provided in the composition, according to the guidance provided by Tazaorac and Angel, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

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by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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

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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(l)(1) - 706.02(l)(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

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more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims with modification due to applicants amendment of claims. is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant

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claims and the '561 application recite a composition (tazarotene) for the treatment of acne. 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.

New Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention. Instant claim 1 use the term "emulsion lotion comprising an oil phase and an aqueous phase", "wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil", "wherein the aqueous phase comprises water and a carbomer homopolymer", "wherein the composition further comprises a polymeric emulsifier", this terminology which has been held to be

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IPR Petition - USP 11,311,482

indefinite. See MPEP § 2173 .05(h)(I) ("If a Markush grouping requires a material selected from an open list of alternatives (e.g., "comprising" or "comprises" the recited alternatives), the claim should generally be rejected under 35 U.S.C. § 112(b) as indefinite because it is unclear what other alternatives are intended to be encompassed by the claim.").

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Claims 1, 6-10, 12 and 27-28 is rejected.

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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 - Thursday 8-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1627

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IPR Petition - USP 11,311,482

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Angel et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	08/05/2020	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	02/23/2021	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	06/07/2021	kc

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	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Angel et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

Search Notes		
Search Notes	**Date**	**Examiner**
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	03/15/2019	KC
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	02/24/2020	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	08/05/2020	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	02/23/2021	kc
INVENTOR	02/23/2021	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	06/07/2021	kc
INVENTOR	06/07/2021	kc

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

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	3	"20190133943".pn.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:19 PM
L2	607207	L1 OR ((A61K31/4436 OR A61K47/14 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61K47/06 OR A61K47/32 OR A61P17/00 OR A61P17/10).cpc.)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:21 PM
L3	6145	L2 AND tazarotene	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:21 PM
L4	3233	L3 AND "mineral oil"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:23 PM
L5	3210	L4 AND water	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:24 PM
L6	212	L5 AND "diethyl sebacate"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:25 PM
L7	135	L6 AND "sorbitan monooleate"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 12:26 PM
L8	200	L1 OR (("ARTURO A".ine. OR "ARTURO; ANGEL".ine. OR "CHOI YOON E".ine. OR "JEON MIN SEO".ine. OR "KIM SOK".ine. OR "PARK YUN HWAN".ine. OR "PILLAI R".ine. OR "PILLAI; RADHAKRISHNAN".ine	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 01:16 PM

		.))					
L9	25	L8 AND tazarotene	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 01:16 PM
L10	0	L9 AND "mineral oil" SAME "water" SAME "poloymeric emulsifer"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/07 01:17 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/179,576
	Filing Date	November 2, 2018
	First Named Inventor	Arturo Angel
	Art Unit	1627
	Examiner Name	Kathrien Ann Cruz
	Attorney Docket Number	095920-004120US-1240999

U.S. PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1.	Medical Review, Part 2. Drug Approval Package for Tazorac (tazarotene cream). Application No.: 021184. Approval Date: 9/29/2000. accessdata.fda.gov/drugsatfda_docs/nda/2000/21-184_Tazorac.cfm.	

EXAMINER SIGNATURE

Examiner Signature	/KATHRIEN A CRUZ/	Date Considered	06/07/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A.C/

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/179,576
	Filing Date	November 2, 2018
	First Named Inventor	Arturo Angel
	Art Unit	1627
	Examiner Name	Kathrien Ann Cruz
	Attorney Docket Number	095920-004120US-1240999

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1.	Medical Review, Part 2. Drug Approval Package for Tazorac (tazarotene cream). Application No.: 021184. Approval Date: 9/29/2000. accessdata.fda.gov/drugsatfda_docs/nda/2000/21-184_Tazorac.cfm.	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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:	Arturo Angel
Filer:	Andrew David Presley/Sharleen Lane
Attorney Docket Number:	095920-004120US-1240999

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:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Padagis Ex. 1029
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	220	220
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**480**

Electronic Acknowledgement Receipt	
EFS ID:	42842589
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:	Arturo Angel
Customer Number:	112120
Filer:	Andrew David Presley/Sharleen Lane
Filer Authorized By:	Andrew David Presley
Attorney Docket Number:	095920-004120US-1240999
Receipt Date:	27-MAY-2021
Filing Date:	02-NOV-2018
Time Stamp:	18:18:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$480
RAM confirmation Number	E20215QI18504047
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	Extension of Time	095920-004120US_EOT.pdf	163956 9f49b9c7191f7e9bf174252860e146fab9c92ebd	no	1
Warnings:					
Information:					
2		095920-004120US_AMD.pdf	240482 03bf46019c60c93c19d2648bc05e468e86db1941	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	13

Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	095920-004120US_132DEC.pdf	369551 45c77ac67eb14a8001a95becc552d6c3bef061c3	no	11
Warnings:					
Information:					
4		095920-004120US_IDS.pdf	223835 74b9a74152 4b5c89c8ed7ea495e90a4da5af50c5	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2

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	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
5	Non Patent Literature	Medical_Review_Part2_Tazorac_21-184.PDF	2202700 9911ed286aaf9832d5a13b645f8122c126b80424	no	32
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	32485 101730f79973d20b8eb4410494f59ab99bc7af8d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3233009		

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.

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 095920-004120US-1240999
Application Number 16/179,576	Filed November 2, 2018
For TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES	
Art Unit 1627	Examiner Kathrien Ann Cruz

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☒ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$220
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$_____
☐ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$_____
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$_____
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$_____

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 69,844

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____

/Andrew Presley/	May 27, 2021
Signature	Date
Andrew D. Presley	(415) 273-4310
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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IPR Petition - USP 11,311,482

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 27, 2021.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877-2-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Cruz

Technology Center/Art Unit: 1627

AMENDMENT / RESPONSE TO OFFICE ACTION

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

Commissioner:

In response to the Office Action mailed February 26, 2021, please enter the following amendments and consider the following remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

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IPR Petition - USP 11,311,482

AMENDMENTS TO THE CLAIMS

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

Listing of Claims:

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~~ at a concentration of 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 comprising an oil phase and an aqueous phase,

wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil,

wherein the aqueous phase comprises water and a carbomer homopolymer,

wherein the composition further comprises a polymeric emulsifier, and

wherein the tazarotene ~~or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion~~ is in solution in the oil phase.

2-5. (Canceled)

6. (Currently amended) 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~~

the dicarboxylic acid ester and the mineral oil are present in a total amount of 10-12 percent by weight of the composition,

the carbomer homopolymer is present in an amount of 0.5-0.7 percent by weight of the composition, and

the polymeric emulsifier is present in an amount of 0.3-0.5 percent by weight of the composition.

7. (Currently amended) The topical pharmaceutical composition of claim 1, wherein [[an]]the dicarboxylic acid ester in the oil phase of the emulsion ~~comprises~~ is diethyl sebacate.

8. (Currently amended) The topical pharmaceutical composition of claim 1, wherein ~~an aqueous phase of the emulsion comprises water and a carbomer homopolymer~~ the composition further comprises sorbitol solution, 70%.

9. (Currently amended) The topical pharmaceutical composition of claim[[1]] 8, 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~~ the sorbitol solution, 70%, is present in an amount of 10-11 percent by weight of the composition.

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

11. (Canceled)

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

13-26. (Canceled)

27. (Previously presented) 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 ±0.5; and

purified water, q.s. to 100 weight %.

28. (Previously presented) 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 ±0.5; and

purified water, q.s. to 100 weight %.

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REMARKS

Upon entry of the present Amendment, claims 1, 6-10, 12, and 27-28 will be pending in this application. Claims 1 and 6-10 are currently amended, and claims 11 and 24-26 are canceled without disclaimer or prejudice to future prosecution. No new matter is added. Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

I. Examiner Interview

At the outset, Applicant would like to thank the Examiner for participating in the telephone interview conducted on May 13, 2021, with Eugenia Garrett-Wackowksi, Esq., Dr. Gordon J. Dow, and the undersigned representative. During the Interview, the rejection of claims under 35 U.S.C. § 103 and the data in the application were discussed. The courtesy of the Examiner's time and consideration is much appreciated.

II. Amendments to the Claims

Claim 1 is amended to recite that the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase; wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil; wherein the aqueous phase comprises water and a carbomer hompolymer; wherein the composition further comprises a polymeric emulsifier; and wherein tazarotene is present in solution in the oil phase. Support for the amendment can be found, for example, in claim 9 as originally filed.

Claim 6 is amended to recite that the dicarboxylic acid ester and the mineral oil are present in a total amount of 10-12 weight %; the carbomer homopolymer is present in an amount of 0.5-0.7 weight %; and the polymeric emulsifier is present in an amount of 0.3-0.5 weight %. Support for the amendment can be found, for example, in claim 27.

Claim 7 is amended to properly depend from claim 1.

Claim 8 is amended to recite that the composition further comprises sorbitol solution, 70%. Claim 9 is amended to recite that the sorbitol solution in present in an amount of 10-11 weight %. Claim 10 is amended to recite that oil phase comprises light mineral oil. Support for the amendments can be found, for example, in claim 27.

The amendments to the claims introduce no new matter, and Applicant respectfully requests that the amendments be entered.

III. Rejection of Claims under 35 U.S.C. § 103

Claims 1, 4, 5-12, and 24-28 are rejected under 35 U.S.C. § 103 as allegedly obvious over Tazorac ("Highlights of Prescribing Information, LABEL (fda.gov), December 2013) in view of Angel *et al.* (WO 2012/087443; "Angel"). To the extent that the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

In the Office Action, it is stated that Tazorac discloses tazarotene cream, 0.05% and 0.1%, for topical use, containing benzyl alcohol, carbomer 1342, carbomer homopolymer type B; edetate disodium; medium chain triglycerides, mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monoleate.[1]

It is acknowledged that Tazorac fails to disclose the amount of tazarotene as presently claimed, the pH of the formulation as presently claimed, and diethyl sebacate, sorbitol solution, methyl paraben, and propyl paraben as presently claimed.[2] However, it is alleged that it would be obvious to combine the disclosure of Tazorac with the disclosure of Angel so as to arrived at the presently claimed lotion composition:

> It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.[3]
>
> One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating a skin disorder consisting of tazarotene would have found in prima facie obvious to administer the concentration of tazarotene in the emulsion of Tazaorac in order to arrive at the instantly claimed emulsion. … the ordinary artisan would have motivated to optimize the workable ranges

[1] Office Action at page 7.
[2] Office Action at page 8.
[3] Office Action at page 9.

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> disclosed by Tazaorac, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolong effect.[4]

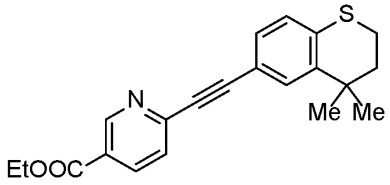
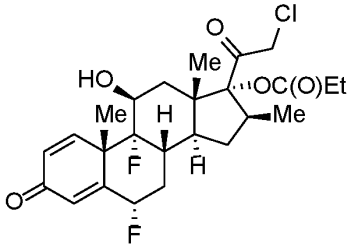
Applicant respectfully disagrees. As discussed during the interview on May 13, 2021 and explained below, one of skill in the art would *not* be motivated to combine the references as suggested in the Office Action and one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed composition.

A. One of skill in the art would not be motivated to combine the cited references.

As noted above, it is alleged that the skilled artisan would be motivated to modify the cream of Tazorac by using diethyl sebacate, sorbitol, and parabens, because Angel discloses that such excipients are useful for enhancing solubility, chemical stability, and penetration properties. Applicant respectfully submits that the skill would *not* be motivated to combine the references as proposed in the Office Action, because the references are directed to two very different active agents. This point was explained in the interview, as well as in the Declaration of Dr. Gordon J. Dow submitted herewith under 37 C.F.R § 1.132 as Exhibit A ("the Declaration").

Dr. Dow, who is named as a co-inventor on the Angel reference, is an expert in the field of formulation development for topical treatment of skin conditions. In the Declaration, Dr. Dow explains that the skilled artisan would *not* be motivated by the disclosure of Angel to modify Tazorac so as to arrive at the claimed lotion composition. Dr. Dow explains that halobetasol propionate, a corticosteroid disclosed by Angel for the treatment of psoriasis, has a vastly different chemical structure and physicochemical properties as compared to tazarotene, a retinoid, disclosed by Tazorac. Some of these differences are tabulated in the Declaration, portions of which are reproduced below. As shown below, the logP values for tazarotene, a retinoid, and halobetasol propionate, a steroid, indicate that tazarotene is almost 1000 times less lipophilic than halobetasol propionate.

[4] Office Action at pages 9-10.

	Tazarotene	Halobetasol propionate
		
Mol. Wt.	351.46	484.96
logP [a]	5.987+/-0.448	2.947+/-0.630

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 at 25 °C.

Dr. Dow explains that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This is because the physicochemical properties of halobetasol propionate, a steroid, are entirely different from the physicochemical properties of tazarotene, a retinoid. Dr. Dow notes that Angel discloses stability data for halobetasol propionate lotion formulations and effective halobetasol propionate delivery via topical administration. However, Dr. Dow explains that the skilled artisan would *not* expect such results to extend to a tazarotene formulation given the considerable differences between the active agents. According to Dr. Dow, the skilled formulator would understand that the stability and delivery considerations for halobetasol propionate could *not* be translated to tazarotene, and the skilled formulator would *not* look to the disclosure of Angel when formulating tazarotene.

Applicant respectfully submits that the cited references do *not* support a case of obviousness as articulated in the Office Action for at least these reasons.

B. The surprising properties of the claimed composition are evidence of non-obviousness.

Dr. Dow also explains that the skilled artisan would *not* expect the surprising advantages of the claimed lotion composition, in terms of tolerability and efficacy, based on the cited references. During the interview, the Examiner noted that the claims are directed to a composition and *not* to a method of treatment. Applicant agrees that this is indeed the case. However, as made clear in the MPEP, "A chemical composition and its properties are

inseparable."[5] The improved efficacy and tolerability of the claimed lotion composition, as compared to TAZORAC cream, result from the components of the lotion as presently claimed. Dr. Dow explains that he and other skilled artisans would not have expected these improved properties based on the teachings of Tazorac and Angel.

Dr. Dow notes that tazarotene and other retinoids are known to cause skin irritation at the site of topical application. Dr. Dow points out that tazarotene is understood to be the most irritating retinoid approved for topical use in acne, and that irritation caused by tazarotene is not a rare occurrence. Rather, it is a real-world clinical problem that is experienced by most acne patients. The irritation is frequently severe enough to negatively impact patient compliance with tazarotene-based treatment regimens. Dr. Dow has reviewed the data in the Application and data available from the U.S. Food & Drug Administration (FDA) for TAZORAC cream. As detailed below, the data show that the claimed tazarotene lotion provides a surprising improvement in both efficacy and tolerability as compared to the known TAZORAC 0.1% and 0.05% creams.

The Application describes a side-by-side comparison of acne treatment using tazarotene 0.045% lotion according to the present claims and TAZORAC 0.1% cream, which was discussed during the interview. Dr. Dow points out in the Declaration that the TAZORAC 0.05% cream is not approved for treating acne. Only the TAZORAC 0.1% cream was approved by the U.S. Food & Drug Administration for treating acne, as reflected in the TAZORAC Prescribing Information. However, clinical study data is available from the FDA's Summary Basis of Approval for TAZORAC 0.05% cream in the treatment of psoriasis. Dr. Dow has reviewed this data, and he has found that is relevant for comparison of the claimed tazarotene 0.045% lotion and the TAZORAC 0.05% cream.

In the Declaration, Dr. Dow highlights the marked improvement in tolerability provided by the claimed tazarotene 0.045% lotion as shown, for example, in Table 8 of the application. Table 8 is reproduced below and tabulates the incidence of adverse events during treatment with tazarotene 0.045% lotion and TAZORAC 0.1% cream.

[5] MPEP § 2112.01(II)

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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%

Table 8 shows that higher tolerability was achieved using tazarotene 0.045% lotion than when using TAZORAC 0.1% cream. The irritation level observed for TAZORAC 0.1% cream was *markedly higher* than the irritation level observed for tazarotene 0.045% lotion according to the present claims ("Composition A"). Dr. Dow notes that the tazarotene 0.045% lotion exhibited very little irritation relative to placebo. Dr. Dow explains that he would not have expected this result, particularly because tazarotene is understood as the most irritating retinoid approved for treating acne as noted above. Applicant notes that Composition A contains the components and quantities recited in present claim 28, and is also closely embraced by claim 27.

Dr. Dow points to the clinical trial data for treating psoriasis with TAZORAC 0.1% cream and TAZORAC 0.05% cream in the FDA's Summary Basis of Approval, which is relevant for assessing the relative tolerability of TAZORAC 0.05% cream and the claimed lotion. A copy of the relevant portion of the Medical Review from the Drug Approval Package for TAZORAC cream is listed in the Information Disclosure Statement submitted herewith.[6] Dr. Dow notes that the 0.05% TAZORAC cream was *as irritating* as the 0.1% TAZORAC cream in key parameters directed to skin-related adverse events. Dr. Dow provides examples of the surprising similarity in the reported incidence of these adverse events for the two concentrations of TAZORAC cream. The reported incidence of erythema, for example, was 17.2% (0.05% TAZORAC cream) vs. 17.9% (0.1% TAZORAC cream) while the reported incidence of burning

[6] Medical Review, Part 2. Drug Approval Package for Tazorac (tazarotene cream). Application No.: 021184. Approval Date: 9/29/2000. accessdata.fda.gov/drugsatfda_docs/nda/2000/21-184_Tazorac.cfm.

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skin was 17.7% (0.05% TAZORAC cream) vs. 16.1% (0.1% TAZORAC cream).[7] Based on these data, Dr. Dow concludes that the unexpected reduction in side effects of the claimed 0.045% tazarotene lotion vs. 0.1% TAZORAC cream is translatable to 0.05% TAZORAC cream. Dr. Dow concludes that the irritation level observed for 0.05% TAZORAC cream would also be *markedly higher* than the irritation level observed for the claimed 0.045% tazarotene lotion.

In the Declaration, Dr. Dow also points to the higher efficacy provided by the claimed 0.045% tazarotene lotion, as compared to TAZORAC cream. This higher efficacy is shown in Table 6 in the Application, which is reproduced below. Table 6 summarizes treatment success for 0.045% tazarotene lotion according to the present claims and 0.01% TAZORAC cream.

Table 6
Treatment % Success (Intention-To-Treat) 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%

Based on this data, Dr. Dow concludes that the improvement over placebo observed for 0.045% tazarotene lotion was substantially higher than the improvement over placebo observed for 0.1% TAZORAC cream. Dr. Dow states that it would be unexpected to obtain even equivalent efficacy, so it was even more surprising that the claimed tazarotene lotion provided *greater* efficacy using *less than half* the dose. Dr. Dow explains that the skilled artisan would *not* expect to increase the efficacy when decreasing the amount by over half. Dr. Dow also explains that he would expect the 0.05% TAZORAC cream to be less effective and more irritating than the 0.045% tazarotene lotion claimed in the Application, when considering the data available for the two TAZORAC creams (*i.e.*, TAZORAC 0.05% and 0.01%). Dr. Dow

[7] Medical Review, Part 2 at page 23.

emphasizes that he would not have expected the dramatic improvement in both the efficacy and tolerability of the claimed lotion based on the disclosures in the cited references.

Applicant respectfully reiterates that the cited references do not support a *prima facie* case of obviousness because one of skill in the art would *not* be motivated to combine the references as suggested in the Office Action due to the vast differences in the chemical structures and physicochemical properties of the active agents. Even if the combination were made in the absence of such motivation, one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed lotion. For at least these reasons, Applicant submits that the claims are *not* obvious over the cited references and respectfully requests that the rejection be withdrawn.

IV. Double Patenting Rejections

The claims are rejected on the grounds of non-statutory obviousness-type double patenting over claims in U.S. Patent Nos. 10,426,787 and 10,251,895, as well as over claims in co-pending Pat. Appl. No. 16/179,561.

The Examiner has not yet indicated that the pending claims are in condition for allowance. As such, the filing of a terminal disclaimer is premature. Applicant therefore respectfully requests, without acquiescing to the validity of these rejections, that the rejections be held in abeyance until the pending claims are in condition for allowance. At that time, Applicants will address the non-statutory double patenting rejections as necessary.

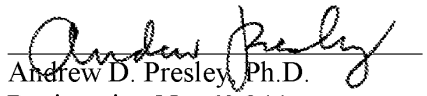
CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (415) 273-4310.

Respectfully submitted,



Andrew D. Presley, Ph.D.
Registration No. 69,844

KILPATRICK TOWNSEND & STOCKTON LLP

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I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 27, 2021.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P0587-2-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 1093
Arturo Angel	Examiner: Kathrien Ann Cruz
Application No.: 16/179,576	Technology Center/Art Unit: 1627
Filed: Nov 2, 2018	
For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES	DECLARATION UNDER 37 C.F.R. § 1.132
Customer No.: 112120	

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

Commissioner:

I, Dr. Gordon J. Dow, declare as follows:

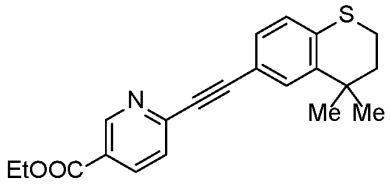
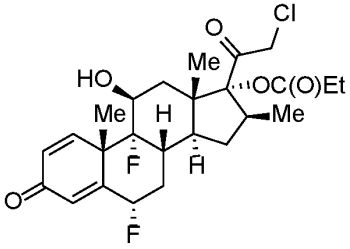
1. I am the founder of Dow Pharmaceutical Sciences, a company providing formulation development, optimization, testing, and manufacturing services to pharmaceutical and biotechnology clients, in 1977. The company is now part of Bausch Health Companies Inc., and I continue to serve the company under a consulting agreement. My areas of specialty include development of dermatological products, particularly acne treatments, corticosteroids, antibiotics, anti-inflammatories, sunscreens, skin bleaches, moisturizers, mild skin cleansers, anti-psoriatics, topical rosacea formulations, photodynamic therapy agents, antipruritics, bath products, anti-wart products and novel topical drug vehicles. I have over 40 years of experience in the field of drug formulation and have overseen and been personally involved with the development of dozens of commercial topical and dermatological pharmaceutical products that

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have been approved by the United States Food and Drug Administration and other regulatory agencies. My curriculum vitae is attached as Exhibit 1.

2. I have read the above-referenced patent application ("the Application"), and I am familiar with the contents of the Application. In addition, I have read the Office Action mailed February 26, 2021, and the claims contained in an Amendment submitted concurrently with this Declaration. It is my understanding that the previously pending claims were rejected as allegedly obvious over the Prescribing Information for TAZORAC® (tazarotene) cream, 0.05% and 0.1% ("TAZORAC") in view of Angel *et al.* (WO 2012/087443; "Angel"). I have read both of the cited references, and I note that I am named as an inventor in the Angel reference.

3. Having reviewed the application and the cited references, and based on my personal experience in the field of topical formulations for treatment of skin conditions, I believe a skilled formulator would *not* find motivation in the disclosure of Angel for modifying TAZORAC so as to arrive at the claimed tazarotene 0.045% lotion. Angel relates to the treatment of psoriasis with halobetasol propionate, a corticosteroid, and I do not believe a skilled formulator would look to this reference for guidance when formulating tazarotene. This is because the two active agents have vastly different chemical structures and physicochemical properties. For example, as summarized below, the logP values for tazarotene and halobetasol propionate indicate that tazarotene is almost 1000 times <u>less</u> lipophilic than halobetasol propionate. In view of tazarotene's much lower lipophilicity and very different chemical structure, I would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate.

	Tazarotene	**Halobetasol propionate**
		
Mol. Wt.	351.46	484.96
logP [a]	5.987+/-0.448	2.947+/-0.630

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 at 25 °C.

4. The physicochemical properties of halobetasol propionate, a steroid, are entirely different from the physicochemical properties of tazarotene, a retinoid. While Angel discloses stability data for halobetasol propionate lotion formulations and effective halobetasol propionate delivery via topical administration, a skilled formulator such as myself would *not* expect such results to extend to a tazarotene formulation given the considerable differences between the active agents. A skilled formulator would understand that the stability and delivery considerations for halobetasol propionate could *not* be translated to tazarotene, and the skilled formulator would *not* look to the disclosure of Angel when formulating tazarotene. Furthermore, nothing in the cited references would lead me to expect that a tazarotene 0.045% lotion would provide the advantages discovered by the inventors of the claimed formulation.

5. Retinoid active agents such as tazarotene are known to be useful for the treatment of skin conditions such as acne and psoriasis, although—as explained in the Application—tazarotene is known to cause skin irritation at the site of topical application. Such irritation is not a rare occurrence, or an issue of mere academic interest. Tazarotene is generally understood to be the most irritating retinoid approved for topical use in acne. Irritation caused by tazarotene is a real-world clinical problem that is experienced by most, if not all, acne patients. The irritation is frequently severe enough to negatively impact patient compliance with tazarotene-based treatment regimens. Having reviewed the data in the Application and data available from the U.S. Food & Drug Administration (FDA) for TAZORAC cream, it is clear to me that the claimed tazarotene lotion provides a surprising improvement in both efficacy and tolerability as compared to the previously known TAZORAC formulations. I would not have expected these improvements, and I do not believe that other skilled formulators would expect these improvements based on the teachings of TAZORAC and Angel.

6. The Application describes a side-by-side comparison of acne treatment using tazarotene 0.045% lotion according to the present claims and 0.1% tazarotene cream (TAZORAC). Notably, the cited TAZORAC Prescribing Information shows that only the 0.1% tazarotene cream was approved by the U.S. Food & Drug Administration for treating acne; the 0.05% tazarotene cream is not approved for treating acne. It is my understanding that the side-by-side comparison was made with TAZORAC at the 0.1% concentration for this reason. However, as discussed further below, clinical study data available from the FDA's Summary

Basis of Approval for TAZORAC in the treatment of psoriasis is informative for comparison of the claimed tazarotene 0.045% lotion and TAZORAC at the 0.05% concentration.

7. The Application shows that, surprisingly, tazarotene 0.045% lotion provides markedly improved tolerability. Table 8 in the Application, reproduced below, summarizes the incidence of adverse events during treatment with tazarotene 0.045% lotion and TAZORAC 0.1%.

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%

8. Table 8 shows that higher tolerability was achieved using tazarotene 0.045% lotion than by using TAZORAC 0.1% cream. The irritation level observed for TAZORAC 0.1% cream was *markedly higher* than the irritation level observed for tazarotene 0.045% lotion according to the present claims. In fact, tazarotene 0.045% lotion exhibited very little irritation relative to placebo. I would not have expected this result, especially when considering that tazarotene is understood as the most irritating retinoid approved for treating acne as noted above.

9. I have reviewed the clinical trial data for TAZORAC 0.1% and TAZORAC 0.05% in the treatment of psoriasis, available in the FDA's Summary Basis of Approval. The data show that 0.05% TAZORAC was *as irritating* as 0.1% TAZORAC in key parameters directed to skin-related adverse events. The reported incidence of these adverse events was surprisingly similar for the two concentrations. The reported incidence of erythema, for example, was 17.2% (0.05% TAZORAC) vs. 17.9% (0.1% TAZORAC) while the reported incidence of burning skin was 17.7% (0.05% TAZORAC) vs. 16.1% (0.1% TAZORAC). Therefore, it is my opinion that the unexpected reduction in side effects of the claimed 0.045% tazarotene lotion vs. TAZORAC 0.1% is translatable to TAZORAC 0.05%. That is to say, the

irritation level observed for TAZORAC 0.05% cream would also be ***markedly higher*** than the irritation level observed for the claimed tazarotene 0.045% lotion.

10. The Application also demonstrates that higher efficacy was achieved using tazarotene 0.045% lotion than by using TAZORAC 0.1% cream. Table 6 in the Application, reproduced below, summarizes treatment success for tazarotene 0.045% lotion according to the present claims ("Composition A") and TAZORAC.

Table 6
Treatment % Success (Intention-To-Treat) 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%

11. This data shows that the improvement over placebo observed for tazarotene 0.045% lotion was substantially higher than the improvement over placebo observed for TAZORAC 0.1% cream. It would have been unexpected to obtain even equivalent efficacy, so it was even more surprising that the claimed tazarotene lotion provided greater efficacy using less than half the dose. A skilled formulator would *not* expect to increase the efficacy when decreasing the amount of the active agent to such an extent. Given the data available for TAZORAC cream 0.05% and 0.01%, I would expect the 0.05% TAZORAC cream to be less effective and more irritating than the 0.045% lotion claimed in the Application. It must be emphasized that nothing in the cited references would lead me to expect that a tazarotene 0.045% lotion would provide the dramatic efficacy and tolerability improvement as demonstrated in the Application.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment; or both, under Section 1001 of Title 18 of the

Padagis Ex. 1029
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United States Code, and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.

Dated: May 12, 2021 By: _____
Gordon J. Dow, Pharm.D.

EXHIBIT 1

Gordon J. Dow, Pharm. D.

40 Corte Amado
Greenbrae, CA 94904
Phone: 707-364-0175
Email: gordon.jay.dow@gmail.com

PROFILE

Gordon Dow, a pharmaceutical scientist whose career focused on dermatological product research and development, founded Dow Pharmaceutical Sciences, Inc. in 1977. The company provided contract services for several hundred domestic and international pharmaceutical firms ranging from start-ups to biotech to large phamra. Services included dermatological formula design, product development, non-clinical safety strategies, clinical trial supplies, Phase I-III clinical evaluations and regulatory filings. A multiple patent holder, Dr. Dow has developed new formulations, ranging from Neutrogena's non-prescription T-Gel shampoo for dandruff to Bausch Health's Jublia, a prescription treatment for onychomycosis. Over the years Dr. Dow has developed a number of unique dermatologicals that have been developed for or acquired by leading dermatological pharmaceutical companies for marketing and distribution in the United States and various world-wide markets.

EXPERTISE

- Invention of dermatological products
- Project management and comprehensive dermatological product development
- Design and formulation of products for skin disease
- Problem-solving concerning dermatologicals and formulation issues
- Technical writing for regulatory submissions (INDs, NDAs)
- Creation of optimized topical drug vehicles for new drug substances
- Creation of comprehensive clinical and regulatory development plans
- Leading product development teams from concept to NDA approval
- Technical consulting and client liaison

Topical formulation and product development experience includes acne treatment products, corticosteroids, antibiotics, anti-inflammatories, sunscreens, skin bleaches, moisturizers, mild skin cleansers, anti-psoriatics, topical rosacea formulations, PDT agents, anti-pruritics, bath products, topical antifungals and anti-wart products. Development work has been conducted on wide range of topical dosage forms such as shampoos, creams, lotions, ointments, gels, solutions, sprays.

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EDUCATION

1961-1965	University of California, San Francisco Doctor of Pharmacy, 1965 Regents Scholar, Rexall Award, Rho Chi Honor Society
1959-1961	University of California, Berkeley

U.S. PATENTS (partial list)

- Patent #4,738,842, Topical Anti-inflammatory Compositions
- Patent #5,061,700, Glyceryl Acetate Ointment Vehicles
- Patent #5,733,886, Compositions of Clindamycin and Benzoyl Peroxide for Acne Treatment
- Patent #5,985,313, Method for decreasing the frequency of transmission of viral infections using cellulose acetate phthalate or hydroxypropyl methylcellulose phthalate excipients
- Patent #6,117,843, Compositions for the Treatment of Acne Containing Clindamycin and Benzoyl Peroxide (II)
- Patent #6,165,493, Methods and compositions for decreasing the frequency of HIV, herpesvirus and sexually transmitted bacterial infections
- Patent #6,387,383, Topical Low-Viscosity Gel Composition
- Patent #6,468,989, Gel Compositions Containing Metronidazole
- Patent #6,517,847, Topical Lotion Delivery System
- Patent #6,589,922, Skin Cleanser Comprising a Steareth, Poloxamer, and a Glyceryl Monoester
- Patent #6,881,726, Aqueous Compositions Containing Metronidazole
- Patent #7,252,816, Topical Acne Vulgaris Medication with a Sunscreen
- Patent #7,300,669, Fluticasone Lotion Having Improved Vasoconstrictor Activity
- Patent #7,326,408, Improving Sunscreen Compliance by Combination with Acne Medication
- Patent #7,348,317, Aqueous Compositions Containing Metronidazole (II)

- Patent #7,368,122, Skin Cream Compositions Comprising Polymeric Emulsifiers
- Patent #7,300,669, Fluticasone Lotion Having Improved Vasoconstrictor Activity
- Patent #7,704,959, Azithromycin for the Treatment of Nodular Acne
- Patent #8,124,123, Controlled Release Azithromycin Solid Dosage Forms
- Patent #8,143,227, Azithromycin for Treatment of Skin Disorders
- Patents #8,288,434 & #10,220,049 Topical Pharmaceutical Formulations Containing a Low Concentration of Benzoyl Peroxide
- Patent #8,809,307, Pharmaceutical formulations containing corticosteroids for topical administration
- Patents #8,663,699, #8,895,070, #9,078,870, #9,504,704, #9,561,208, #9,693,988, #10,137,142, #10,220,049, and #10,624,918, Topical pharmaceutical formulations containing a low concentration of benzoyl peroxide in suspension in water and a water miscible organic solvent
- Patents #9,616,123, #9,925,194, and #10,166,235, Kinetin/Zeatin Topical Formulations
- Patent #9,744,150, Suspension containing micronized benzoyl peroxide
- Patent, Topical Pharmaceutical Formulations Containing a Low Concentration of Benzoyl Peroxide
- Patent #10,245,257, and 10,828,293 Anti-infective methods, compositions, and devices
- Patents #10,251,895, and #10,426,787, Topical Compositions and Methods for Treatment of Psoriasis

PUBLICATIONS

Gordon Dow, Yunik Chang, Sarmistha Basu and Karen Yu. A Novel Aqueous Metronidazole Gel 1% with Hydro-Solubilizing Agents. American Academy of Dermatology, Summer Meeting. Poster No. P27. July 2005, Chicago.

Gordon Dow, David Osborne, Sarmistha Basu and Arturo Angel. Comparison of Topical Vehicles: Aesthetic and User Preference Parameters. American Academy of Dermatology 63rd Annual Meeting. Poster No. P403. February 2005, New Orleans.

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Daniel Bucks, Steffany Gaffagan, Krista Witt and Gordon Dow. Significance of Formulation Composition on Clindamycin Release from Gels and Corresponding Clinical Utility. American Academy of Dermatology Annual Meeting. March 2003, San Francisco.

PRESENTATIONS

"The Art and Science of Formulating Vaginal Microbicides," NIAID (NIH) Topical Microbicides Development and Evaluation Workshop, March 20, 2003, Washington, DC.

"Formulating Dermatologicals," Workshop - Topical Dermatological Development in the USA, June 4, 2009, New Brunswick, NJ.

"Formulating Dermatologicals for Regulatory, Clinical and Commercial Success," AGAH Workshop – Dermatological Product Development, May 25, 2008, Hamburg, Germany.

"The Magic Formulations – What Dermatologists Need to Know," CME at South Beach Symposium, January 15, 2010, Miami, FL.

EMPLOYMENT HISTORY

2011 - 2015	Retired. Consultant to Dow Pharmaceutical Sciences, Inc.
1977 – 2011	Dow Pharmaceutical Sciences, Inc. (DPSI); Founder & President, and then Chief Technical Officer. The company provided consulting and contract topical product development services to other companies, as well as developing its own dermatological products for out-licensing. January 2009 DPSI became a wholly owned subsidiary of Valeant Pharmaceuticals International now known as Bausch Health).
1981 – 2004	Allerderm Laboratories; Founder and CEO. Provided strategic direction to the General Manager of this marketer/distributor of dermatological devices such as hypoallergenic devices and contact dermatitis products. Allerderm was sold to SmartHealth in 2004.
1973 - 1984	State of California; Executive Secretary of the Research Advisory Panel, the office that authorizes and monitors schedule I drug research and drug abuse treatment research. Reviewed research protocols, conducted site visits of research programs for cancer patients, and conducted day-to-day business of the regulatory agency responsible for controlled substances research.
1965 - 1973	Ingram Pharmaceutical Company, a regional specialty firm focused on dermatology products, (later acquired by Syntex); Product

Development Scientist and then Vice President, Research & Development. Developed seven commercial products. Also involved in manufacturing, quality control and technical support for sales and customer service.

PRODUCT DEVELOPMENT INVOLVMENT IN COMMERCIAL PRODUCTS

- Aldara
- T-Gel Shampoo
- Carmol 20 Cream, Carmol 10 Lotion and Carmol HC Cream
- Abreva
- Clindagel (1% clindamycin) Gel
- OC-8
- Clinac BPO Gel
- Avita Gel
- Lubrex Cream and Cleanser
- Condylox Solution
- Desonate 0.05% Gel
- Metrogel (metronidazole) 1% Gel
- Ziana (clindamycin 1% and Tretinoin 0.025%) Gel
- Clobex (clobetasol propionate 0.05%)
- Acanya (benzoyl peroxide 2.5% and clindamycin 1%) Gel
- Jublia (10% efinaconazole) Solution
- Atralin Gel (0.05% tretinoin)
- Bryhali (0.01% halobetasol propionate) Lotion

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I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 27, 2021.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Cruz

Technology Center/Art Unit: 1627

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. In accordance with the provisions of 37 CFR §1.98(a)(2), copies of any cited U.S. Patents and U.S. Patent Application Publications are not provided. Copies of the remaining cited references are provided.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

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As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

The Commissioner is authorized to charge the fee set forth in §1.17(p) to the firm's credit card for consideration of this paper. The Commissioner is authorized to charge any additional fee due to Deposit Account No. 20-1430.

Respectfully submitted,

Andrew D. Presley, Ph.D.
Registration No. 69,844

KILPATRICK TOWNSEND & STOCKTON LLP

74824307V.1

Attachment

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/27/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 9	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Arturo Angel	095920-004120US-1240999	1093

112120 7590 05/18/2021

Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER	
CRUZ, KATHRIEN ANN	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/18/2021	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):

KTSDocketing2@kilpatrick.foundationip.com
ipefiling@kilpatricktownsend.com

PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	Application No. 16/179,576	Applicant(s) Angel et al.		
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (First Inventor to File) Status Yes	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
KATHRIEN A CRUZ	Primary Examiner	WebEx/Video Conference
ANDEW PRESLEY	Attorney	
EUGENIA WACKOWSKI	Attorney	
GORDON DOW	Inventor	

Date of Interview: 13 May 2021

Issues Discussed:

35 U.S.C. 103

Applicants assert that tazaorac at low dose would not been expected to have more efficacy. The examiner disagrees because the Tazaorac specifically discloses 0.5%. Therefore, it would have been obvious to optimize said composition to 0.045% from a dose of 0.05% as disclosed by Tazaorac with a reasonable expectation of success absence evidence to the contrary. Applicants assert that the properties are inseparateble per Mr. Presley. Discussed the possibility claim amendments. Mr. Dow and Mr. Presley refers to table 6 and states that it demonstrates unexpected results. The examiner would like to respectively remind applicants that Tazaorac specifically discloses a composition of tazaotene at a concentration of 0.05% which is 50% less than the compared concentration of table 6.

/KATHRIEN A CRUZ/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Apr 26 2021

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Andrew D. Presley

S-signature:
/Andrew Presley/

Registration Number:
69844

U.S. Application Number:
16179576

Confirmation Number:
1093

E-mail Address:
apresley@kilpatricktownsend.com

Phone Number:
+1 4152734310

Proposed Time of Interview:
5-5-2021 3:00 PM ET

Alternative Proposed Time(s) of Interview:
5-5-2021 3:30 PM ET

Alternative Proposed Time(s) of Interview:
5-5-2021 4:00 PM ET

Prefered Interview Type:
Video Conference

I am the applicant or applicant's representative for this application.

Topic for Discussion:
Rejection of claims under 35 USC 103

uspto UNITED STATES PATENT AND TRADEMARK OFFICE

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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

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	1627	2180	095920-004120US-1240999	23	2

CONFIRMATION NO. 1093

UPDATED FILING RECEIPT

112120
Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

OC000000124978708

Date Mailed: 04/20/2021

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

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

Applicant(s)

BAUSCH HEALTH US, LLC, Bridgewater, NJ;

Power of Attorney: The patent practitioners associated with Customer Number 112120

Domestic Priority data as claimed by applicant

This application is a CIP of 15/977,088 05/11/2018 ABN
and is a CIP of 15/173,961 06/06/2016 PAT 10251895
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

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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.

Projected Publication Date: Not Applicable

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 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).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/179,576	11/02/2018	Arturo Angel	095920-004120US-1240999

CONFIRMATION NO. 1093

112120
Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

37 CFR 1.48(f)
ACKNOWLEDGEMENT LETTER

OC000000124978710

Date Mailed: 04/20/2021

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 04/15/2021.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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**.

/rmohamed/

Padagis Ex. 1029
IPR Petition - USP 11,311,482

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/179,576	11/02/2018	Arturo Angel	095920-004120US-1240999

CONFIRMATION NO. 1093

112120
Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

POA ACCEPTANCE LETTER

OC000000124978686

Date Mailed: 04/20/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/15/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

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**.

/rmohamed/

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207 CIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Angel~~ Arturo		~~Arturo~~ Angel	

Residence Information (Select One) ● US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
Santa Rosa	CA	US

Mailing Address of Inventor:

Address 1	4953 Sheleen Court
Address 2	
City	Santa Rosa
State/Province	CA
Postal Code	95409
Country i	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	State/Province	Country of Residence
Santa Rosa	CA	US

Mailing Address of Inventor:

Address 1	5787 Owl Hill Avenue
Address 2	
City	Santa Rosa
State/Province	CA
Postal Code	95409
Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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~~ 112120		
Email Address	~~patent@hselaw.com~~ ipefiling@kilpatricktownsend.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~~ 095920-004120US-1240999	**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~~ 112120		

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~39336.000207-CIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data 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-GIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~39336.000207-CIP~~095920-004120US-1240999
	Application Number	16/179,576
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.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~095920-004120US-1240999
	Application Number	16/179,576
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	Joint Inventor
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~~ BAUSCH HEALTH US, LLC		
Mailing Address Information For Applicant:			
Address 1	400 Somerset Corporate Boulevard		
Address 2			
City	Bridgewater	**State/Province**	NJ
Country	US	Postal Code	08807
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:

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

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 Presley/			Date (YYYY-MM-DD)	2021-04-12
First Name	Andrew D.	Last Name	Presley	Registration Number	69,844

Additional Signature may be generated within this form by selecting the Add button. Add

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~39336.000207-CIP~~ 095920-004120US-1240999
	Application Number	16/179,576
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.**

Electronic Acknowledgement Receipt

EFS ID:	42468834
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 David Presley/Sharleen Lane
Filer Authorized By:	Andrew David Presley
Attorney Docket Number:	99336.000342
Receipt Date:	15-APR-2021
Filing Date:	02-NOV-2018
Time Stamp:	19:47:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	095920-004120US_CorrectedADS_ApplicationNumberADDED.pdf	562276 866b2a61d9457971ee74a38325ea01f96aff05be	no	8
Warnings:					

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Information:	
This is not an USPTO supplied ADS fillable form	
Total Files Size (in bytes):	562276

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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Doc Code: R48.REQ
Document Description: Request under Rule 48 correcting inventorship

PTO/AIA/40 (04-18)
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U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)		
	Application Number	16/179,576
	Filing Date	November 2, 2018
	First Named Inventor	Arturo Angel
	Art Unit	1627
	Examiner Name	CRUZ, KATHRIEN ANN
	Practitioner Docket Number	095920-004120US-1240999

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

Applicant hereby **requests that the inventorship be corrected or changed, or that the name of the inventor or a joint inventor, or the order of the names of joint inventors, be changed,** in the above-identified application. **Note**: 37 CFR 1.48 applies to any request to correct inventorship filed on or after September 16, 2012, regardless of the application filing date. **Do not submit this form after payment of the issue fee or if the application has been patented.** See 37 CFR 1.324 for correction of inventorship in a patent.

Please check the applicable box(es) below.

For a nonprovisional application:

☐ 1. This request is to correct or change the inventorship in a **nonprovisional** application (**under 37 CFR 1.48(a)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the Manual of Patent Examining Procedure (MPEP) section 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☐ The processing fee set forth in 37 CFR 1.17(i). $ _____

☐ An inventor is being added. An inventor's oath or declaration by any actual inventor who has not yet executed an oath or declaration is required (see 37 CFR 1.48(b)). See MPEP 602.01(a) for information about an inventor's oath or declaration for an application filed on/after September 16, 2012 (*e.g.*, form **PTO/AIA/01**). For information about an inventor's oath or declaration for an application filed before September 16, 2012 (*e.g.*, form **PTO/SB/01**), see MPEP 602.01(b).

☐ This request is being filed after the first Office action on the merits has been given or mailed (see 37 CFR 1.48(c) and 1.17(d)). Check one of the following:

☐ This request to correct or change the inventorship is due solely to the cancellation of claims in the application.

OR

☐ The fee set forth in 37 CFR 1.17(d) is due (in addition to the fee set forth in 37 CFR 1.17(i)). $ _____

This collection of information is required by 37 CFR 1.48. 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 1.11 and 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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IPR Petition - USP 11,311,482

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U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

■ 2. This request is to correct or update the name of the inventor or a joint inventor, or the order of names of joint inventors, in a **nonprovisional** application (**under 37 CFR 1.48(f)**) and includes:

■ An application data sheet in accordance with 37 CFR 1.76(c) identifying the complete inventive entity, including the corrected or updated name of the inventor, or the new order of names shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the MPEP 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

■ The processing fee set forth in 37 CFR 1.17(i). $ 140

For a provisional application:

☐ This request is to change or correct the inventorship, or correct or update the name of the inventor or a joint inventor, in a **provisional** application (**under 37 CFR 1.48(d)**) and includes:

☐ **Attached hereto** is a document that is signed by a party set forth in 37 CFR 1.33(b) and identifies each inventor by his or her legal name, in the preferred order. Note: the document may be an application data sheet in accordance with 37 CFR 1.76(c) that identifies the changes with markings (underlining for insertions, strikethrough for deletions).

☐ The processing fee set forth in 37 CFR 1.17(q). $ _____

Fee Payment Information:

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

■ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 20-1430.

■ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ Applicant*

■ attorney or agent of record
Registration number 69,844

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Andrew Presley/

Typed or printed name Andrew D. Presley

Date April 12, 2021

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☐ ** Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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 inspection 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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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 David Presley/Sharleen Lane
Attorney Docket Number:	99336.000342

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:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	140

Electronic Acknowledgement Receipt	
EFS ID:	42465362
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 David Presley/Sharleen Lane
Filer Authorized By:	Andrew David Presley
Attorney Docket Number:	99336.000342
Receipt Date:	15-APR-2021
Filing Date:	02-NOV-2018
Time Stamp:	15:38:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$140
RAM confirmation Number	E20214EF40201096
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Padagis Ex. 1029
IPR Petition - USP 11,311,482

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Req to correct/update/change appl name until pay issue fee	095920-004120US_Rule46_changeApplicant.pdf	194127 69e859f7241375c1b4d30165133ad61ea8731121	no	2
Warnings:					
Information:					
2	Application Data Sheet	095920-004120US_CorrectedADS.pdf	553164 3b3a16fa18313d06ddfa61ce379b87d30660ae73	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Assignee showing of ownership per 37 CFR 3.73	095920-004120US_Statement373.pdf	113578 aebcfc5d75b4f3bcbea9f2ab749b5add2177d2ff	no	3
Warnings:					
Information:					
4	Power of Attorney	095920-004120US_POA82A_POA82B.pdf	261521 9c212fae6a47f840dc9fbfee1a812cffd7430753	no	2
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
5	Oath or Declaration filed	095920-004120US_Declaration_Angel.pdf	133388 e57df7332a7c0f04c32eb86fe1d3fd7846b7ce7d	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					

Padagis Ex. 1029
IPR Petition - USP 11,311,482

6	Oath or Declaration filed	095920-004120US_Declaration_Pillai.pdf	986915 97bc35aa71e114387f03dbe4687255deec3e2614	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
7	Request under Rule 48 correcting inventorship	095920-004120US_Rule48_correctInventorName.pdf	1025004 66e0ca912000360ec14ff5701a5b96a05ab900c7	no	3
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30446 6cd408f4ccac996597d037f1b6f7c6bed298450a	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3298143	

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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Doc Code: R46C.REQ
Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST TO CORRECT OR UPDATE THE NAME OF THE APPLICANT UNDER 37 CFR 1.46(c)(1), OR CHANGE THE APPLICANT UNDER 37 CFR 1.46(c)(2)

(FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER SEPTEMBER 16, 2012)

Application Number	16/179,576
Filing Date	November 2, 2018
First Named Inventor	Arturo Angel
Art Unit	1627
Examiner Name	CRUZ, KATHRIEN ANN
Practitioner Docket Number	095920-004120US-1240999

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

Applicant hereby **requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2),** in the above-identified application. **Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.**

Please check the applicable box(es) below.

☐ 1. This request is to **correct or update the name of the applicant** (**under 37 CFR 1.46(c)(1)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (*i.e.*, where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

■ 2. This request is to **change the applicant** (**under 37 CFR 1.46(c)(2)**) and includes:

■ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

■ A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

☐ applicant* ■ attorney or agent of record Registration number 69,844 ☐ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Andrew Presley/

Typed or printed name Andrew D. Presley

Date April 12, 2021

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☐ ** Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. 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 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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 inspection 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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207 CIP~~ 095920-004120US-1240999
	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.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Angel~~ Arturo		~~Arturo~~ Angel	

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	5787 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

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~ 095920-004120US-1240999
	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~~ 112120		
Email Address	~~patent@hselaw.com~~ ipefiling@kilpatricktownsend.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~~ 095920-004120US-1240999	**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~~ 112120		

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~39336.000207-CIP~~ 095920-004120US-1240999
	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).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~ 095920-004120US-1240999
	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.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~095920-004120US-1240999
	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.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~095920-004120US-1240999
	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	Joint Inventor
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~~ BAUSCH HEALTH US, LLC		
Mailing Address Information For Applicant:			
Address 1	400 Somerset Corporate Boulevard		
Address 2			
City	Bridgewater	**State/Province**	NJ
Country	US	Postal Code	08807
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:

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~99336.000207-CIP~~ 095920-004120US-1240999
	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:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

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 Presley/			Date (YYYY-MM-DD)	2021-04-12
First Name	Andrew D.	Last Name	Presley	Registration Number	69,844

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~39336.000207-CIP~~ 095920-004120US-1240999
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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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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: BAUSCH HEALTH US, LLC

Application No./Patent No.: 16/179,576 Filed/Issue Date: November 2, 2018

Titled: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

BAUSCH HEALTH US, LLC, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 055829, Frame 0075, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). 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 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application 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**.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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IPR Petition - USP 11,311,482

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Andrew Presley/	April 12, 2021
Signature	Date
Andrew D. Presley	69,844
Printed or Typed Name	Title or Registration Number

[Page 2 of 2]

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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 inspection 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.

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IPR Petition - USP 11,311,482

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	16/179,576
Filing Date	November 2, 2018
First Named Inventor	Arturo Angel
Title	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
Art Unit	1627
Examiner Name	CRUZ, KATHRIEN ANN
Attorney Docket Number	095920-004120US-1240999

SIGNATURE of Applicant or Patent Practitioner

Signature	/Andrew Presley/	Date (Optional)	April 12, 2021
Name	Andrew D. Presley	Registration Number	69,844
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)	BAUSCH HEALTH US, LLC		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 112120

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box)

BAUSCH HEALTH US, LLC

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Suzanne L. Hamilton/	Date (Optional)	March 24, 2021
Name	Suzanne L. Hamilton		
Title	Sr. Legal IP Specialist and Authorized Signatory		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

■ United States application or PCT international application number 16/179,576 filed on November 2, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Arturo Angel Date (Optional): April 12, 2021

Signature: Arturo Angel

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/179,576 filed on November 2, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Radhakrishnan Pillai Date (Optional): April 12, 2021

Signature: R Radhakrishnan

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application 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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000342	1093

134756 7590 02/26/2021

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

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
02/26/2021	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

Office Action Summary	Application No. 16/179,576	Applicant(s) Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 6/25/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,6-12 and 24-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,6-12 and 24-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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, 4, 6-12, 24-28 is pending.

Upon careful consideration and in view of the decision of the pre-appeal, it has been determine to reopen prosecution. Therefore, the presently presented rejection is a non-final rejection.

Action Summary

Claims 1, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over Angel et al (WO2012/087443 published 06/28/2012) and Donello (U.S. Publication 2012/0328670) Bershad et al (WO2000/047211 published 08/17/2000) and Jackson (WO2012/061630 published 05/10/2012) all are of record withdrawn.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787 is maintained.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895 is maintained.

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Claims 1, 6-12, 24-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561 is maintained.

Response to Arguments

Argument with regards to Donello, Bershad and Jackson are moot since none of these art is used in the presently rejection.

Applicants argue that no where in the cited art discloses or suggestion of a tazarotene oil-in-water emulsion or consisting essentially of as recited in instant claim 28. And that Angel teaches halobetasol and not tazarotene. This argument has been fully considered but has not been found persuasive. Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE)

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diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

Applicants argue that Angel is drawn to a corticosteroid composition whereas the instant claims are drawn to tazarotene composition. This argument has been fully considered but has not been found persuasive. Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each

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gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a

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diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

Applicant argue that obvious double patenting rejection over the issue is not what the applications may or may not recite, but whether the instant claims would have been obvious from the claims of the '787 patent. The claims of the '787 patent are specifically directed towards a method of treating psoriasis (not acne as alleged) employing a composition comprising tazarotene and halobetasol propionate as combined active agents. While it is true that the '787 patent is treat psoriasis and the instant application is treating acne; however, both are skin disease and are treated with the very same active agent (e.g. tazarotenic acid). Therefore, both the instant application and the '787 patent possess overlapping scopes of inventions.

Applicant argue that obvious double patenting rejection over the issue is not what the applications may or may not recite, but whether the instant claims would have been obvious from the claims of the '895 patent. The claims of the '895 patent are specifically directed towards a method of treating psoriasis (not acne as alleged) employing a composition comprising tazarotene and halobetasol propionate as combined active agents. While it is true that the '895 patent is treat psoriasis and the instant application is treating acne; however, both are skin disease and are treated with the very same active agent (e.g. tazarotenic acid). Therefore, both the instant application and the '787 patent possess overlapping scopes of inventions.

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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, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) of record.

Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). (11, under Description).

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Tazaorac does not disclose diethyl sebacate, sorbitol solution, methyl and propyl paraben nor the concentrations of the inactive agents. Tazaorac does not disclose the pH.

Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0 (table 4). Angel exemplify a 0.01 %wt. a formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

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It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating a skin disorder consisting of tazarotene would have found it prima facie obvious to administer the concentration of tazarotene in the emulsion of Tazaorac in order to arrive at the instantly claimed emulsion. Tazaorac teaches the concentration of tazaotene of 0.05% and 0.1% contains 0.5 and 1 mg. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree,

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or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the workable ranges disclosed by Tazaorac, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazaorac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to the of concentrations of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% as disclosed by Angel. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of

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administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the workable ranges disclosed by Tazaorac and Angel, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% provided in the composition, according to the guidance provided by Tazaorac and Angel, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is

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noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards the limitation "wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion", since it is known in the art that the composition is in an oil-in-water emulsion as disclose by Angel, it would have been obvious that in order to obtain the oil-in-water emulsion, the active agent would have been dissolved in an oil. Furthermore, the instant claims are drawn to a method of treating acne not a method of preparing said composition.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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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(l)(1) - 706.02(l)(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).

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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, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy

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to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims 1, 6-12, 24-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '561 application recite a composition (tazarotene) for the treatment of acne. 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.

Conclusion

Claims 1, 6-12, 24-28 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 - Thursday 8-6pm.

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Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1627

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Notice of References Cited	Application/Control No. 16/179,576	Applicant(s)/Patent Under Reexamination Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	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					
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	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	Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013)
	V	
	W	
	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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	08/05/2020	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	02/23/2021	kc

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	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

Search Notes		
Search Notes	**Date**	**Examiner**
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	03/15/2019	KC
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	02/24/2020	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	08/05/2020	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	02/23/2021	kc
INVENTOR	02/23/2021	kc

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

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	0	"il in water" SAME lotion	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/22 04:51 PM
L2	2	"20140336161"	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/22 06:07 PM
L3	3	"20190133943".pn.	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:23 PM
L4	567473	L3 OR ((A61K31/4436 OR A61K47/14 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61K47/06 OR A61K47/32 OR A61P17/00 OR A61P17/10).cpc.)	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:27 PM
L5	5309	L4 AND tazarotene	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:28 PM
L6	279	L5 AND "diethyl sebacate"	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:28 PM
L7	189	L6 AND "mineral oil"	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:29 PM
L8	119	L7 AND "sorbitan monooleate"	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:29 PM
L9	40	L8 AND @py<2015	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO;	OR	ON	ON	2021/02/23 03:29 PM

			DERWENT; IBM_TDB				
L10	190	L3 OR (("ARTURO A".ine. OR "ARTURO; ANGEL".ine. OR "CHOI YOON E".ine. OR "JEON MIN SEO".ine. OR "KIM SOK".ine. OR "PARK YUN HWAN".ine. OR "PILLAI R".ine. OR "PILLAI; RADHAKRISHNAN".ine.))	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:30 PM
L11	24	L10 AND tazarotene	US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	ON	2021/02/23 03:30 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000342	1093

134756 7590 01/15/2021

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

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
01/15/2021	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 Panel Decision from Pre-Appeal Brief Review	Application No.	Applicant(s)	
	16/179,576	Arturo et al.	
	Examiner	Art Unit	AIA (FITF) Status
	Mark L Shibuya	1624	Yes

This is in response to the Pre-Appeal Brief Request for Review filed 10 December 2020 .

1. ☐ **Improper Request** - The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: _____ .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☐ **Proceed to Board of Patent Appeals and Interferences** - A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☐ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____ .
Claim(s) objected to: _____ .
Claim(s) rejected: _____ .
Claim(s) withdrawn from consideration: _____ .

3. ☐ **Allowable application** - A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☑ **Reopen Prosecution** - A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) MARK L SHIBUYA .	(3) TQAS BENNETT CELSA .
(2) KATHRIEN CRUZ .	(4) _____ .

/MARK L SHIBUYA/
Supervisory Patent Examiner
Art Unit 1624

U.S. Patent and Trademark Office
PTOL-2297 (Rev. 02/11)

Part of Paper No. 20210112

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Confirmation No.: 1093

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Angel Arturo
Applicant:	Valeant Pharmaceuticals North America
Application No.:	16/179,576
Filed:	November 2, 2018
Examiner:	CRUZ, Kathrien Ann
Group/Art Unit:	1621
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

December 10, 2020

Dear Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicant requests review of the final rejection in the above identified application. No amendments are being filed with this request. This request is being filed with a notice of appeal. No more than five (5) pages of arguments are submitted herewith.

Fee-Charge Authorization

By way of precaution, the Commissioner is authorized to charge any 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 the Notice of Appeal and this Request.

PRE-APPEAL BRIEF REQUEST FOR REVIEW ARGUMENTS

I. Rejection of claims 1, 4, 6-12, and 24-28 under 35 U.S.C. § 103 as being unpatentable over Angel et al (WO2012/087443), Donello (U.S. Publication 2012/0328670), Bershad et al (WO2000/047211) and Jackson (WO2012/061630)

Applicant respectfully traverses this rejection with respect to the present claims because the cited references do not teach or suggest a topical pharmaceutical composition meeting all of the combined limitations of independent claims 1 and 28. More particularly, the final rejection is in clear error, as the Examiner has mischaracterized the actual teachings of the cited references, and has failed to establish a *prima facie* case of obviousness based on combining the actual teachings of the various cited references so as to result in the present claimed invention without the improper use of hindsight reconstruction based on Applicant's own teachings.

1.1 Nowhere in any of Angel, Donello, Bershad and Jackson is there any teaching or suggestion of a tazarotene oil-in-water emulsion having a tazarotene concentration of 0.045% as the sole active pharmaceutical ingredient, wherein the tazarotene is dissolved in a liquid oil component of the emulsion as recited in independent claim 1, or a composition having a tazarotene concentration of 0.045% and consisting essentially of the further components as recited in independent claim 28.

Regarding Angel, rather than be directed towards tazarotene compositions as claimed in the present application, such disclosure is specifically directed towards corticosteroid compositions comprising one or more esters of monocarboxylic and dicarboxylic acids, and the Examiner acknowledges that Angel discloses compositions consisting of halobetasol propionate as the active ingredient. Angel does not disclose any active ingredients other than steroids, and thus provides no teaching with respect to tazarotene compositions.

Regarding Donello, such disclosure teaches compositions comprising a retinoid (which may be tazarotenic acid or pharmaceutically acceptable salt) as sole active agent, where such compositions are in the form of particles comprising biodegradable polymer and the retinoid. Thus, Donello does not teach or suggest compositions wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of an emulsion.

Regarding further cited Bershad, there is no support for the Examiner's characterizations at page 11, lines 6-13 of the Final Rejection that Bershad specifically teaches topical emulsions consisting of tazarotene in claims 1-5 (or a tazarotene topical emulsion at page 2 lines 15-30), or topical oil-in-water emulsions, nor "[t]he retinoid tazarotene, in concentrations of 0.025-1% wt. of the composition" at cited page 4, lines 25-30, and page 7, lines 20-25. Rather, Bershad is silent with respect to any oil-in-water emulsion formulations, and appears to only refer to commercial gel formulations at page 1, lines 25-31,

and generally to a gel, cream, lotion, ointment, cleanser, or solution at cited page 7, lines 15-20. Further, while Bershad discloses the amounts of retinoid (in general) in the disclosed compositions can range from about 0.01% to about 10% by weight, or preferably from about 0.025% to about 1-5% by weight at page 7, lines 20-25, Bershad more specifically teaches in such cited passage that therapeutically effective amounts depend on the specific retinoid and its bioavailability and goes on to say that "[f]or tazarotene, commercially available preparations of 0.05% and 0.1% are effective." No other specific concentrations of tazarotene are suggested, and especially not specific concentrations in an oil-in-water emulsion formulation. While Bershad teaches that tazarotene emulsions at the lower commercially available concentration of 0.05% wt. results in adverse skin effects, Bershad does not teach further lowering the concentration of tazarotene applied to reduce side effects while maintaining efficacy, but rather teaches to reduce contact time to overcome topical side effects (e.g., employing a short duration from 30 seconds to 30 minutes, or preferably from 5 to 10 minutes), and that "following the prescribed period of time, the skin is rinsed thoroughly" to reduce the adverse effects of retinoids. Bershad; p. 2, line 25; p. 3, lines 13-14; and p. 7, lines 20-23). Thus, the Examiner's statements as to the teachings of Bershad are clearly mischaracterizations of the actual disclosure thereof, and instead Bershad provides no teaching specifically with respect to tazarotene that concentrations lower than 0.05% in an oil-in-water emulsion formulation would be expected to provide good efficacy.

Regarding Jackson, such reference discloses combining a retinoid with an imidazoquinoline compound to increase the penetration of the latter (see Jackson; e.g., paragraphs 0009-0010). Tazarotene is unremarkably disclosed among 19 retinoids. Although the tazarotene concentration in such combinations is disclosed generally in the range of 0.001-1% wt., or 0.025-1%, or 0.01-0.5% (see Jackson; e.g, paragraph 0024), Jackson does not suggest use of tazarotene at such range of concentrations as a sole active pharmaceutical ingredient for any purpose. Thus, Jackson does not motivate one of ordinary skill to employ tazarotene at any concentration as a sole active pharmaceutical ingredient, and in particular, at or near the lower end of Jackson's ranges for use as a sole active ingredient with a reasonable expectation of success, let alone of enabling improved combination of efficacy and low adverse events in the treatment of acne as demonstrated in the examples of the present invention.

1.2 The proposed combination of references clearly go against the actual teachings of the cited references, and is not based on the actual teachings thereof.

The Examiner argues at page 6, lines 8-15 that "Taking the cited art, it would have been obvious to combine tazarotenic acid as the sole agent in the treatment of acne in view of Angel," that "it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello," and that it "would have been obvious to substitute tazarotenic acid because tazarotenic acid is known in the art (e.g. Donello) as a sole agent to

treat acne." Contrary to such assertions, Angel is specifically directed towards corticosteroid compositions, not tazarotenic acid. Further, as Donello is specifically directed towards compositions comprising particles of biodegradable polymer and a retinoid, it would go against the teachings of each of such references to substitute tazarotenic acid for the corticosteroid of Angel (as Angel is instead specifically directed towards corticosteroid compositions) which might be dissolved in a liquid oil component in Angel (as Donello is specifically directed towards particulate formulations). Thus, as such combination clearly goes against the actual teachings of each reference, it is clearly only proposed based on improper hindsight reconstructions, rather than the actual teachings of the cited references.

1.3 The Examiner's mischaracterizations further evidence the rejection is based on improper hindsight reconstruction based on Applicant's own teachings.

Regarding the further erroneous assertions by the Examiner relative to the actual teachings of Bershad and Jackson, such mischaracterizations evidence that the Examiner has used Applicant's claims as a template for reconstruction based on impermissible hindsight reconstruction using isolated pieces of information in the prior art, rather than based on only the actual teachings of the prior art. Applicant thus respectfully submits the asserted rejection is based on mischaracterizations and clear errors, and that the combination of Angel, Donello, Bershad, and Jackson accordingly does not establish a *prima facie* case of obviousness. Rather, based on their actual teachings such references do not in combination teach or suggest a composition necessarily having all of the limitations of each of claims 1, 4, 6-12, and 24-28, without relying upon impermissible hindsight reconstruction and without going against the actual teachings of each individual reference. While the Examiner asserts it "would have been obvious to employ tazarotenic acid as the sole agent in the treatment of acne in view of Angel," as explained above Angel is actually specifically directed towards the use of corticosteroids such as halobetasol propionate, and substitution of an entirely different class of active agent would thus go against the actual teachings of Angel, and not be *prima facie* obvious. Angel's teachings are solely with respect to use of corticosteroids, and there would be no reasonable expectation of success for use of an entirely different class of pharmaceutical active agents such as retinoids and in particular tazarotene in the formulations thereof.

1.4 The Examiner's further proposed motivation "in order to arrive at the instantly claimed invention" further fails to support a prima facie case of obviousness.

The Examiner further alleges at page 12 of the Final Rejection that one of ordinary skill in the art would have found it obvious to lower the concentration of tazarotene in the "emulsion of Donello in view of Bershad in order to arrive at the instantly claimed emulsion." Such assertion is not well-supported, as neither Donello or Bershad actually teach an oil-in-water emulsion formulation as claimed, and rather Donello is instead specifically directed towards formulations comprising particles of biodegradable polymer and a retinoid. The Examiner's assertions that the motivation for lowing the

concentration of tazarotene would be "in order to arrive at the instantly claimed invention" is further evidence that the asserted rejection is made using impermissible hindsight reconstruction based on Applicant's own teachings, rather than only the actual teachings of the cited references. While the Examiner further asserts at page 13 of the Final Rejection that one skilled in the art would have been motivated to lower the concentration of tazarotene in Donello based on Bershad in order to avoid adverse side effects while maintaining efficacy at treating psoriasis, there is no such teaching in Bershad, which rather teaches a reduced contact time to overcome topical side effects as explained above (e.g., Bershad; p. 2, line 25; p. 3, lines 13-14; and p. 7, lines 20-23), with no disclosure, teaching or suggestion as to maintaining efficacy at lower concentrations.

Thus, in view of the distinct actual teachings of each of the asserted prior art relative to the present claimed invention (i.e., Angel is specifically directed towards corticosteroid formulations, not tazarotene; Donello is specifically directed towards formulations comprising particles of biodegradable polymer and retinoid, not oil-in-water emulsions wherein tazarotene is dissolved in a liquid oil component of an oil-in-water emulsion; Bershad teaches reduced contact time, not reduced concentrations of tazarotene to avoid adverse side effects while maintaining efficacy; and Jackson is specifically directed towards formulations comprising a retinoid in combination with an imidazoquinoline compound, not tazarotene as a sole active pharmaceutical agent), it is clear that the asserted rejection is based on mischaracterizations of the actual teachings of the cited references, as well as picking and choosing from among distinct individual teachings or disclosures in each reference, in an impermissible hindsight manner based at least in significant part on Applicant's own teachings, rather than only the actual teachings of the cited references. See, e.g., *In re Wesslau*, 53 C.C.P.A. 746, 750; 353 F.2d 238, 241; 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965) ("It is impermissible within the framework of § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art."). Accordingly, a proper *prima facie* case of obviousness of independent claims 1 and 28 (and all claims dependent thereon) has not been established.

II. Rejections of claims 1, 4, 6-12, and 24-28 on the ground of nonstatutory double patenting

Claims 1, 4, 6-12 and 24-28 were rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-10 of US 10,426,787 and claims 1-10 of US 10,251,895. The Examiner asserts the claims are not patentably distinct from each other because "both application recite the administration of tazarotene to treat acne," with the difference between the instant application and each of the '787 and the '895 patents is that the '787 and the '895 patents also recites halobetasol, but the instant claims "do not preclude a combination therapy to treat acne," and that thus, the instant application and each of the '787 and '895 patents "possess significant overlapping scopes of invention." These rejections are in clear error, as the issue is not what the applications may or may not recite, but

whether the instant claims would have been obvious from the claims of either of the '787 or '895 patents.

The claims of the '787 patent are specifically directed towards a method of treating psoriasis employing a composition comprising tazarotene and halobetasol propionate as combined active agents, and the claims of the '895 patent are specifically directed towards a pharmaceutical composition for treating psoriasis comprising tazarotene and halobetasol propionate as combined active ingredients. The present application claims, conversely, are specifically directed towards a composition comprising tazarotene as a sole pharmaceutical active agent. Thus, instead of having "significant overlapping scopes of invention" as mischaracterized by the Examiner, it is clear to one skilled in the art that the referenced patent claims and the instant application claims are instead clearly directed towards non-overlapping, mutually distinct claimed inventions, and accordingly would not have been obvious in view of each other.

III. Provisional rejection of claims 1, 4, 6-12, and 24-28 on the ground of nonstatutory double patenting

Claims 1, 4, 6-12, and 24-28 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. As this is a provisional rejection, 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, as no claims have yet been indicated as otherwise being allowable.

Conclusion

As a proper *prima facie* case of obviousness has not been made, withdrawal of this rejection and allowance of the application is accordingly respectfully urged.

Respectfully submitted,

/Andrew J. Anderson/

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

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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:	99336.000342

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:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
NOTICE OF APPEAL	1401	1	840	840
Post-Allowance-and-Post-Issuance:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	220	220
Miscellaneous:				
		Total in USD ($)		**1060**

Electronic Acknowledgement Receipt	
EFS ID:	41352066
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:	99336.000342
Receipt Date:	10-DEC-2020
Filing Date:	02-NOV-2018
Time Stamp:	15:59:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1060
RAM confirmation Number	E2020B0F59152380
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	Notice of Appeal Filed	99336-342_Notice_of_Appeal.pdf	348979 7ac6472816aa715d77d1269baa9b78ab0a9fc2a4	no	2
Warnings:					
Information:					
2	Pre-Brief Conference request	99336-342_PreAppealBriefRequest.pdf	231168 54b0be3670e5b08605f3e35415ad712291203837	no	6
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32707 eab5c6410db6e928efc4965c90360e513808a039	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	612854		

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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PTO/AIA/31 (03-14)
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NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional): 99336.000342

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, on Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____.

Signature _____

Typed or printed name _____

In re Application of: Valeant Pharmaceuticals International, Inc.

Application Number	Filed
16/179,576	November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Art Unit	Examiner
1627	Cruz, Kathrien Ann

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 840.00

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 03-3875.

☑ Payment made via EFS-Web.

☑ A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed.
For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant

☐ attorney or agent of record
Registration number _____

☑ attorney or agent acting under 37 CFR 1.34
Registration number 33,564

Signature /Andrew J. Anderson/

Typed or printed name Andrew J. Anderson

Telephone Number 585-231-1157

Date December 10, 2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.20(b)(1) and 41.31. 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 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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.
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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 inspection 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000342	1093

134756 7590 08/10/2020

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

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/10/2020	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

Office Action Summary	Application No. 16/179,576	Applicant(s) Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 6/25/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,6-12 and 24-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,6-12 and 24-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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, 4, 6-12, 24-28 is pending.

Applicants response filed 6/25/2020 has been received and entered in the application.

Action Summary

Claims 1, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over Angel et al (WO2012/087443 published 06/28/2012) and Donello (U.S. Publication 2012/0328670) Bershad et al (WO2000/047211 published 08/17/2000) and Jackson (WO2012/061630 published 05/10/2012) all are of record is maintained.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787 is maintained.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895 is maintained.

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Claims 1, 6-12, 24-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561 is maintained.

Response to Arguments

Applicants argue that no where in the cited art discloses or suggestion of a tazarotene oil-in-water emulsion or consisting essentially of as recited in instant claim 28. And that Angel teaches halobetasol and not tazarotene. This argument has been fully considered but has not been found persuasive. Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid. Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid Tazarotene, in concentration of 0.025-1% wt. of the composition. Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and

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light mineral oil based formulations. Bershad further teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention. Taking the cited art, it would have been obvious to combine tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello. Additionally, since tazarotenic acid is known in the art to effectively treat acne as a sole agent, it would have been obvious to substitute tazarotenic acid because tazarotenic acid is known in the art (e.g. Donello) as a sole agent to treat acne with a reasonable expectation of success.

Applicants argue that Angel is drawn to a corticosteroid composition whereas the instant claims are drawn to tazarotene composition. This argument has been fully considered but has not been found persuasive. Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid. Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid Tazarotene, in concentration of 0.025-1% wt. of the composition. Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid

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ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations. Bershad further teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention. Taking the cited art, it would have been obvious to combine tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello. Additionally, since tazarotenic acid is known in the art to effectively treat acne as a sole agent, it would have been obvious to substitute tazarotenic acid because tazarotenic acid is known in the art (e.g. Donello) as a sole agent to treat acne with a reasonable expectation of success.

Applicants argue that Donello is non-obvious based on the actual teachings of Angel and Donello. This argument has been fully considered but has not been found persuasive. Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid. Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid

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Tazarotene, in concentration of 0.025-1% wt. of the composition. Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations. Bershad further teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention. Taking the cited art, it would have been obvious to combine tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello. Additionally, since tazarotenic acid is known in the art to effectively treat acne as a sole agent, it would have been obvious to substitute tazarotenic acid because tazarotenic acid is known in the art (e.g. Donello) as a sole agent to treat acne.

Applicants argue that Bershad, Donello and Angel and the way that the examiner's has constructed the rejection is impermissible hindsight in several ways and varying statements. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

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reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants argue that Jackson does not suggest use of tazarotene in such a range as a sole active pharmaceutical indredient for any purpose. This argument has been fully considered but has not been found persuasive. Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid. Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid Tazarotene, in concentration of 0.025-1% wt. of the composition. Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations. Bershad further teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention. Taking the cited art, it would have been obvious to combine tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is

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effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello. Additionally, since tazarotenic acid is known in the art to effectively treat acne as a sole agent, it would have been obvious to substitute tazarotenic acid because tazarotenic acid is known in the art (e.g. Donello) as a sole agent to treat acne with a reasonable expectation of success.

Applicant argue that obvious double patenting rejection over the issue is not what the applications may or may not recite, but whether the instant claims would have been obvious from the claims of the '787 patent. The claims of the '787 patent are specifically directed towards a method of treating psoriasis (not acne as alleged) employing a composition comprising tazarotene and halobetasol propionate as combined active agents. While it is true that the '787 patent is treat psoriasis and the instant application is treating acne; however, both are skin disease and are treated with the very same active agent (e.g. tazarotenic acid). Therefore, both the instant application and the '787 patent possess overlapping scopes of inventions.

Applicant argue that obvious double patenting rejection over the issue is not what the applications may or may not recite, but whether the instant claims would have been obvious from the claims of the '895 patent. The claims of the '895 patent are specifically directed towards a method of treating psoriasis (not acne as alleged) employing a composition comprising tazarotene and halobetasol propionate as combined active agents. While it is true that the '895 patent is treat psoriasis and the instant application is treating acne; however, both are skin disease and are treated with the very same active agent (e.g. tazarotenic acid). Therefore, both the instant application and the '787 patent possess overlapping scopes of inventions.

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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, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over Angel et al (WO2012/087443 published 06/28/2012) and Donello (U.S. Publication 2012/0328670) Bershad et al (WO2000/047211 published 08/17/2000) and Jackson (WO2012/061630 published 05/10/2012) all are of record.

Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties of halobetasol propionate when halobetasol is present in a concentration lower than 0.05% wt., while limiting systemic side effects of the super-potent halobetasol (page 1-2, pages 5-6, page 12, lines 1-5,

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page 19, Table 7, claims 1 and 26). Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19).

	% w/w	
Ingredients	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0 - 6.0	pH 4.0 - 6.0
Purified Water, q.s. ad	100	100

As shown in Formula 4a above, Angel exemplify a 0.01 %wt. halobetasol-propionate formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of halobetasol-propionate (0.01%wt.), diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

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Angel does not teach tazarotenic acid.

Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid (claim 11-12).

Bershad and coworkers teach topical emulsions consisting of tazarotene for the treatment of psoriasis (claims 1-5). Bershad teaches that tazarotene emulsions comprising 0.05% wt. result in adverse skin side effects (pruritus, erythema) (page 1 line 30 through page 2 line 20). Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid Tazarotene, in concentration of 0.025-1% wt. of the composition (page 4, lines 25-30, page 7, lines 20-25). MPEP 2144.05 states that "[I]n the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped.). In the instant case, the claimed 0.045%wt. tazarotene lies inside the disclosed 0.025-1% wt. tazarotene of Bershad above. Bershad further

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teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention (page 7 line 15-20).

Jackson and coworkers teaches topical creams and lotions comprising overlapping 0.01-0.05% wt. tazarotene concentrations of Donello and Bershad above ([0024], [0090]). Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations (page 32-33).

It would have been obvious to employ tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating a skin disorder consisting of tazarotene would have found it prima facie obvious to lower the concentration of tazarotene in the emulsion of Donello in view of Bershad in order to arrive at the instantly claimed emulsion. Bershad teaches that tazarotene emulsions comprising 0.05% wt. result in adverse skin side effects (pruritus, erythema), and suggests reducing the concentration of tazarotene to 0.025% wt. as a

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mechanism to overcome the topical side effects above (page 2 lines 15-30 (page1 line 30 through page 2 line 30, page 4 lines 25-30, page 7, lines 20-25). Accordingly, one of ordinary skill in the art would have been motivated to lower the concentration of tazarotene in Donello in order to avoid the adverse side effects of pruritus, erythema while maintaining efficacy at treating psoriasis.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating psoriasis consisting of tazarotene would have found it prima facie obvious to formulate the reduced concentration of tazarotene as taught by Bershad above with the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil as taught by Jackson in order to arrive at the instantly claimed composition. Motivation to formulate the tazarotene-consisting topical formulation with the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil flows logically from the fact that tazarotene transdermal compositions with 0.01-0.05% wt. of the active retinoid comprise advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations (page 32-33).

With regards the limitation “wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion”, since it is known in the art that the composition is in an oil-in-water emulsion as disclose by Angel, it would have been obvious that in order to obtain the oil-in-water emulsion, the active agent would have been dissolved in an oil. Furthermore, the instant claims are drawn to a method of treating acne not a method of preparing said composition.

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For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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

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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(l)(1) - 706.02(l)(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.

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Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims 1, 6-12, 24-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '561 application recite a composition (tazarotene) for the treatment of acne. Taken that both applications disclose the same compound (tazarotene) to treat acne, one of ordinary skills in the art

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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.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Claims 1, 6-12, 24-28 is rejected.

No claims are allowed.

Communication

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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 - Thursday 8-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1627

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	08/05/2020	kc

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
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	02/24/2020	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	08/05/2020	kc

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	11	"10426787"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:36
L2	3	((("ARTURO") near3 ("Angel")) and (("PILLAI") near3 ("Radhakrishnan"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L3	3	L2	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L4	10,103	tazarotene	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L5	3,579	L4 and acne	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L6	2,707	L5 and @py<"2017"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L7	556	L6 and "acne vulgaris"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L8	556	L7	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2020/08/05 12:45
L9	556	L8	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45
L10	2	"20190133942".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:45

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L11	121,604	(A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10).CPC.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:46
L12	60	L11 and "tazaroten"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:47
L13	6	l12 and acne	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/08/05 12:47

EAST Search History (Interference)

<This search history is empty>

8/5/2020 12:47:57 PM
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Confirmation No.: 1093

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Angel Arturo
Applicant:	Valeant Pharmaceuticals North America
Application No.:	16/179,576
Filed:	November 2, 2018
Examiner:	CRUZ, Kathrien Ann
Group/Art Unit:	1621
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

Amendment

Dear Sir:

In response to the Office action dated February 27, 2020, please consider Applicant's amendments and remarks, as shown below.

Amendments to the Specification: none.

Amendments to the Claims begin at page 2 of this paper.

Amendments to the Drawings: none.

Remarks begin at page 6 of this paper.

This Amendment is filed with a petition for, and fee payment of, a one-month extension to the shortened statutory period for reply recited in the above referenced Office Action. Should the undersigned representative be mistaken as to time or fee, please consider this petition for whatever extension of time is necessary to effect this Amendment and/or charge Deposit Account No. 03-3875 of Harter Secrest & Emery LLP for any required deficiency.

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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 at a concentration of 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, and wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion.

2. **(cancelled)**

3. **(cancelled)**

4. **(cancelled)**

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.**(Previously presented)** 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.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

26.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

27.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

28.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

REMARKS

In response to the Office Action of February 27, 2020, the present application has been carefully reviewed and amended. Entry of the present amendment and reconsideration of the application are respectfully requested.

By this Amendment, claim 1 has been amended to include the features of dependent claim 4, and claim 4 has accordingly been cancelled. Claims 2, 3, 5 and 13-23 have previously been cancelled. Accordingly, claims 1, 6-12 and 24-28 are currently pending in this application. No new matter has been added by this Amendment.

Status of Claims

Claims 1, 4, 6-12 and 24-28 were rejected under 35 U.S.C. 103 as being unpatentable over Angel et al (WO2012/087443) and Donello (U.S. Publication 2012/0328670) Bershad et al (WO2000/047211) and Jackson (WO2012/061630).

Claims 1, 4, 6-12 and 24-28 were rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787.

Claims 1, 4, 6-12 and 24-28 were rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895.

Claims 1-4, 6-12 and 24-28 are provisionally rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561.

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

Rejection of claims 1, 4, 6-12, and 24-28 under 35 U.S.C. § 103 as being unpatentable over Angel, Donello, Bershad and Jackson

To demonstrate that a claim is obvious, the party asserting invalidity must present evidence that all limitations of the claim are taught or suggested 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 any of Angel, Donello, Bershad and Jackson is there teaching or suggestion of a tazarotene oil-in-water emulsion having a tazarotene concentration of 0.045% as the sole active pharmaceutical ingredient, wherein the tazarotene is dissolved in a liquid oil component of the emulsion as recited in independent claim 1, or a composition having a tazarotene concentration of 0.045% and consisting essentially of the further components as recited in independent claim 28.

To the contrary, regarding Angel, such disclosure is specifically directed towards corticosteroid compositions comprising one or more esters of monocarboxylic and dicarboxylic acids, and the Examiner acknowledges that Angel discloses compositions consisting of halobetasol propionate as the active ingredient. Angel does not disclose any active ingredients other than steroids, and thus provides no teaching with respect to tazarotene compositions.

Regarding Donello, while such disclosure teaches compositions comprising a retinoid (which may be tazarotenic acid or pharmaceutically acceptable salt) as sole active agent, such compositions are in the form of particles comprising biodegradable polymer and the retinoid. Thus, Donello does not teach or suggest at least the claimed feature of wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion, and accordingly does not teach or suggest all of the limitations of independent claims 1 and 28. Further, as Angel is specifically directed towards corticosteroid compositions, and Donello is specifically directed towards compositions comprising particles of biodegradable polymer and a retinoid, it would go against the teachings of Donello to modify the disclosed compositions to be in the form of an oil in water emulsion as might be taught for the corticosteroid compositions of Angel, rather than polymer particles comprising the retinoid. Consequently, the unique formulations of independent claims 1 and 28 are clearly nonobvious based on the actual teachings of Angel and Donello.

Regarding further cited Bershad, there is no support for the Examiner's characterizations that Bershad specifically teaches topical emulsions consisting of tazarotene in claims 1-5 (or a tazarotene topical emulsion at page 2 lines 15-30), or topical oil-in-water emulsions at page 7

lines 15-20, nor "[t]he retinoid tazarotene, in concentrations of 0.025-1% wt. of the composition" at cited page 4, lines 25-30, and page 7, lines 20-25. Rather, Bershad is silent with respect to any oil-in-water emulsion formulations, and appears to only refer to commercial gel formulations at page 1, lines 25-31, and generally to a gel, cream, lotion, ointment, cleanser, or solution at cited page 7, lines 15-20. Further, while Bershad discloses the amounts of retinoid (in general) in the disclosed compositions can range from about 0.01% to about 10% by weight, or preferably from about 0.025% to about 1-5% by weight at page 7, lines 20-25, Bershad more specifically teaches in such cited passage that therapeutically effective amounts depend on the specific retinoid and its bioavailability and goes on to say that "[f]or tazarotene, commercially available preparations of 0.05% and 0.1% are effective." No other specific concentrations of tazarotene are suggested, and especially not specific concentrations in an oil-in-water emulsion formulation. While Bershad teaches that tazarotene emulsions even at the lower commercially available concentration of 0.05% wt. results in adverse skin effects, Bershad does not teach further lowering the concentration of tazarotene applied to reduce side effects while maintaining efficacy, but rather teaches to reduce contact time to overcome topical side effects (e.g., employing a short duration from 30 seconds to 30 minutes, or preferably from 5 to 10 minutes, and that "following the prescribed period of time, the skin is rinsed thoroughly" to reduce the adverse effects of retinoids. Bershad; p. 2, line 25; p. 3, lines 13-14; and p. 7, lines 20-23). Thus, Bershad provides no teaching such that tazarotene concentrations lower than 0.05% in an oil-in-water emulsion formulation would be expected to provide good efficacy. The erroneous assertions by the Examiner relative to the actual teachings of Bershad suggests that the Examiner has used Applicant's claims as a template for reconstruction based on impermissible hindsight reconstruction using isolated pieces of information in the prior art, rather than based on only the actual teachings of the prior art.

Regarding Jackson, such reference discloses combining a retinoid with an imidazoquinoline compound to increase the penetration of the latter (see Jackson; e.g., paragraphs 0009-0010). Tazarotene is unremarkably disclosed among 19 retinoids. Although the tazarotene concentration in such combinations is disclosed generally in the range of 0.001-1% wt., or 0.025-1%, or 0.01-0.5% (see Jackson; e.g, paragraph 0024), Jackson does not suggest use of tazarotene at such range of concentrations as a sole active pharmaceutical ingredient for

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any purpose. Thus, Jackson does not motivate one of ordinary skill to employ tazarotene at any concentration as a sole active pharmaceutical ingredient, and in particular, at or near the lower end of Jackson's ranges for use as a sole active ingredient with a reasonable expectation of success, let alone of enabling improved combination of efficacy and low adverse events in the treatment of acne as demonstrated in the examples of the present invention.

Additionally, the Examiner asserts that Jackson teaches "formulation of tazarotene in the liquid oil components comprising the dicarboxylic ester (DCAE) diethyl sebacate and light mineral oil," citing paragraph [0124] and claims 1, 58-60. Applicant respectfully traverses this assertion. Jackson never teaches the combination of diethyl sebacate and light mineral oil. Instead, Jackson teaches only 50:50 mixture of isostearic acid and diethyl sebacate or 50:50 mixture of isostearic acid and mineral oil (not even light mineral oil). Jackson; Tables 7 and 8; and paragraph [0124] ("compositions of imiquimod and tazarotene in ISA plus . . . diethyl sebacate, or mineral oil . . ..). Such erroneous assertion by the Examiner again suggests that the Examiner has used Applicant's claims as a template for reconstruction based on impermissible hindsight reconstruction using isolated pieces of information in the prior art, rather than only the actual teachings of the prior art.

Applicant thus respectfully traverses this rejection because the combination of Angel, Donello, Bershad, and Jackson does not establish a *prima facie* case of obviousness as such references based on their actual teachings do not in combination teach or suggest a composition necessarily having all of the limitations of each of claims 1, 4, 6-12, and 24-28, without relying upon impermissible hindsight reconstruction and without going against the actual teachings of each individual reference. While the Examiner asserts it "would have been obvious to employ tazarotenic acid as the sole agent in the treatment of acne in view of Angel," as explained above Angel is actually specifically directed towards the use of corticosteroids such as halobetasol propionate, and substitution of an entirely different class of active agent would thus go against the actual teachings of Angel, and not be *prima facie* obvious. Angel's teachings are solely with respect to use of corticosteroids, and there would be no reasonable expectation of success for use of an entirely different class of pharmaceutical active agents such as retinoids and in particular tazarotene in the formulations thereof.

The Examiner further alleges that one of ordinary skill in the art would have found it obvious to lower the concentration of tazarotene in the "emulsion of Donello in view of Bershad in order to arrive at the instantly claimed emulsion." Such assertion is not well-supported, as neither Donello or Bershad actually teach an oil-in-water emulsion formulation as claimed, and rather Donello is instead specifically directed towards formulations comprising particles of biodegradable polymer and a retinoid. The Examiner's assertions that the motivation for lowing the concentration of tazarotene would be "in order to arrive at the instantly claimed invention" is further evidence that the asserted rejection is made using impermissible hindsight reconstruction based on Applicant's own teachings, rather than only the actual teachings of the cited references. While the Examiner further asserts one skilled in the art would have been motivated to lower the concentration of tazarotene in Donello based on Bershad in order to avoid adverse side effects while maintaining efficacy at treating psoriasis, there is no such teaching in Bershad, which rather teaches a reduced contact time to overcome topical side effects as explained above (e.g., Bershad; p. 2, line 25; p. 3, lines 13-14; and p. 7, lines 20-23), with no disclosure as to maintaining efficacy at lower concentrations.

Thus, in view of the distinct actual teachings of each of the asserted prior art relative to the present claimed invention (i.e., Angel is specifically directed towards corticosteroid formulations, not tazarotene; Donello is specifically directed towards formulations comprising particles of biodegradable polymer and retinoid, not oil-in-water emulsions wherein tazarotene is dissolved in a liquid oil component of an oil-in-water emulsion; Bershad teaches reduced contact time, not reduced concentrations of tazarotene to avoid adverse side effects while maintaining efficacy; and Jackson is specifically directed towards formulations comprising a retinoid in combination with an imidazoquinoline compound, not tazarotene as a sole active pharmaceutical agent), it is clear that the asserted rejection is based on mischaracterizations of the actual teachings of the cited references, as well as picking and choosing from among distinct individual teachings or disclosures in each reference, in an impermissible hindsight manner based at least in significant part on Applicant's own teachings, rather than only the actual teachings of the cited references. See, e.g., *In re Wesslau*, 53 C.C.P.A. 746, 750; 353 F.2d 238, 241; 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965) ("It is impermissible within the framework of § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of

other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art."). Accordingly, a proper *prima facie* case of obviousness has not been established, and withdrawal of this rejection and allowance of the present claims is urged.

Rejection of claims 1, 4, 6-12, and 24-28 on the ground of nonstatutory double patenting

Claims 1, 4, 6-12 and 24-28 were rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. The Examiner asserts the claims are not patentably distinct from each other because "both application recite the administration of tazarotene to treat acne," with the difference between the instant application and the '787 patent is that the '787 patent also recites halobetasol, but the instant claims "do not preclude a combination therapy to treat acne," and that thus, the instant application and the '787 patent possess significant overlapping scopes of invention." This rejection is respectfully traversed, as the issue is not what the applications may or may not recite, but whether the instant claims would have been obvious from the claims of the '787 patent. The claims of the '787 patent are specifically directed towards a method of treating psoriasis employing a composition comprising tazarotene and halobetasol propionate as combined active agents, while the present application claims are specifically directed towards a composition comprising tazarotene as a sole pharmaceutical active agent. Thus, instead of having "significant overlapping scopes of invention" as asserted by the Examiner, it is clear to one skilled in the art that such claims are instead clearly directed towards non-overlapping, mutually distinct inventions, and accordingly would not have been obvious in view of each other.

Claims 1, 4, 6-12 and 24-28 were rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. The Examiner asserts the claims are not patentably distinct from each other because "both application recite the administration of tazarotene to treat acne," with the difference between the instant application and the '895 patent is that the '895 patent also recites halobetasol, but the instant claims "do not preclude a combination therapy to treat acne," and that thus, the instant application and the '895 patent possess significant overlapping scopes of invention." This rejection is respectfully traversed, as the issue is not what the applications may or may not recite, but whether the instant

claims would have been obvious from the claims of the '895 patent. The claims of the '895 patent are specifically directed towards a pharmaceutical composition for treating psoriasis comprising tazarotene and halobetasol propionate as combined active ingredients, while the present application claims are specifically directed towards a composition comprising tazarotene as a sole pharmaceutical active agent. Thus, instead of having "significant overlapping scopes of invention" as asserted by the Examiner, it is clear to one skilled in the art that such claims are instead clearly directed towards non-overlapping, mutually distinct inventions, and accordingly would not have been obvious in view of each other.

Claims 1, 4, 6-12, and 24-28 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. As this is a provisional rejection, 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, as no claims have yet been indicated as otherwise being allowable.

CONCLUSION

In view of the amendments and remarks having addressed all of the objections raised by the Examiner, reconsideration and allowance is courteously requested.

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.

Extension of Time

Applicant petitions for a one-month Extension of Time. The required fee accompanies this reply.

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

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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:	99336.000342
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:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	39827954
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:	99336.000342
Receipt Date:	25-JUN-2020
Filing Date:	02-NOV-2018
Time Stamp:	14:34:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$200
RAM confirmation Number	E20206OE34171060
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_to_OA.pdf	190747 c431e163360be629ffedb2110355b4ded0900c84	yes	13
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	13	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31118 2362940faa222e54348212a9a56bba21cfb6e2c2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	221865		

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.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/25/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 13	Minus	** 23	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000342	1093

134756 7590 02/27/2020

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

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
02/27/2020	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

Office Action Summary	Application No. 16/179,576	Applicant(s) Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/28/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,4,6-12 and 24-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,4,6-12 and 24-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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, 4, 6-12, 24-28 is pending.

Applicants response filed 1/28/2020 has been received and entered in the application.

Upon careful consideration, the final rejection dated 10/28/2019 is hereby vacated. However, a new rejection is made below.

Action Summary

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) is withdrawn.

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) is withdrawn.

Response to Arguments

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Applicant's arguments with respect to claims 1, 4, 6-12 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection.

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, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over Angel et al (WO2012/087443 published 06/28/2012) and Donello (U.S. Publication 2012/0328670) Bershad et al (WO2000/047211 published 08/17/2000) and Jackson (WO2012/061630 published 05/10/2012) all are of record.

Angel teaches topical emulsions for treating psoriasis (e.g. skin disorders) consisting of halobetasol propionate as the active ingredient. Angel exemplifies topical halobetasol propionate lotions in the claimed 0.01% wt. of the emulsion (Example 4A, page 19, Table 3). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility,

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chemical stability and penetration properties of halobetasol propionate when halobetasol is present in a concentration lower than 0.05% wt., while limiting systemic side effects of the super-potent halobetasol (page 1-2, pages 5-6, page 12, lines 1-5, page 19, Table 7, claims 1 and 26). Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19).

	% w/w	
Ingredients	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0 - 6.0	pH 4.0 - 6.0
Purified Water, q.s. ad	100	100

As shown in Formula 4a above, Angel exemplify a 0.01 %wt. halobetasol-propionate formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of halobetasol-propionate (0.01%wt.), diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed

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amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

Angel does not teach tazarotenic acid.

Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid (claim 11-12).

Bershad and coworkers teach topical emulsions consisting of tazarotene for the treatment of psoriasis (claims 1-5). Bershad teaches that tazarotene emulsions comprising 0.05% wt. result in adverse skin side effects (pruritus, erythema) (page 1 line 30 through page 2 line 20). Bershad teaches a short-contact regimen with a tazarotene topical emulsion to overcome the topical side effects above (page 2 lines 15-30). The retinoid Tazarotene, in concentration of 0.025-1% wt. of the composition (page 4, lines 25-30, page 7, lines 20-25). MPEP 2144.05 states that "[I]n the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5%

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thus the ranges overlapped.). In the instant case, the claimed 0.045%wt. tazarotene lies inside the disclosed 0.025-1% wt. tazarotene of Bershad above. Bershad further teaches that topical oil-in-water emulsions including lotions and creams are encompassed in the invention (page 7 line 15-20).

Jackson and coworkers teaches topical creams and lotions comprising overlapping 0.01-0.05% wt. tazarotene concentrations of Donello and Bershad above ([0024], [0090]). Jackson and coworkers teach formulation of tazarotene in the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil ([0124], claims 1, 58-60). As shown in Tables 7-8, tazarotene comprises advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations (page 32-33).

It would have been obvious to employ tazarotenic acid as the sole agent in the treatment of acne in view of Angel. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Angel and Donello with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating a skin disorder consisting of tazarotene would have found it prima facie obvious to lower the concentration of tazarotene in the emulsion of Donello in view of Bershad in order to arrive at the instantly claimed emulsion. Bershad teaches that

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tazarotene emulsions comprising 0.05% wt. result in adverse skin side effects (pruritus, erythema), and suggests reducing the concentration of tazarotene to 0.025% wt. as a mechanism to overcome the topical side effects above (page 2 lines 15-30 (page1 line 30 through page 2 line 30, page 4 lines 25-30, page 7, lines 20-25). Accordingly, one of ordinary skill in the art would have been motivated to lower the concentration of tazarotene in Donello in order to avoid the adverse side effects of pruritus, erythema while maintaining efficacy at treating psoriasis.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions for treating psoriasis consisting of tazarotene would have found it prima facie obvious to formulate the reduced concentration of tazarotene as taught by Bershad above with the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil as taught by Jackson in order to arrive at the instantly claimed composition. Motivation to formulate the tazarotene-consisting topical formulation with the liquid oil components comprising the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil flows logically from the fact that tazarotene transdermal compositions with 0.01-0.05% wt. of the active retinoid comprise advantageous solubility and chemical stability when dissolved/formulated in the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulations (page 32-33).

With regards the limitation “wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion”, since it is known in the art that the composition is in an oil-in-water emulsion as disclose by Angel, it would have been obvious that in order to obtain the oil-in-water emulsion, the active agent would have

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been dissolved in an oil. Furthermore, the instant claims are drawn to a method of treating acne not a method of preparing said composition.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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

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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(l)(1) - 706.02(l)(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

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more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 4, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 4, 6-12, 24-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims 1-4, 6-12, 24-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '561 application recite

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a composition (tazarotene) for the treatment of acne. 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.

Conclusion

Claims 1-4, 6-12, 24-28 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 - Thursday 8-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1627

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

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
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	02/24/2020	kc

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	((("ARTURO") near3 ("Angel")) and (("PILLAI") near3 ("Radhakrishnan"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:31
L2	3	L1	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:31
L3	9754	tazarotene	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:34
L4	3471	L3 and acne	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:34
L5	2707	L4 and @py<"2017"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:34
L6	556	L5 and "acne vulgaris"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:34
L7	556	L6	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 14:34
L8	2	"20120328670"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 15:31
L9	5	"2012087443"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2020/02/24 15:34

EAST Search History (Interference)

<This search history is empty>

2/24/2020 4:20:14 PM
C:\Users\kcruz\Documents\EAST\Workspaces\16179561.wsp

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☑ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	01/28/2020							
	Total (37 CFR 1.16(i))	* 14	Minus	** 23	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT								
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ANGELA D JOHNSON/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Confirmation No.: 1093

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Angel Arturo
Applicant:	Valeant Pharmaceuticals North America
Application No.:	16/179,576
Filed:	November 2, 2018
Examiner:	CRUZ, Kathrien Ann
Group/Art Unit:	1621
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

AMENDMENT AND RESPONSE TO OFFICE ACTION UNDER 37 C.F.R § 1.116

Dear Sir:

In response to the Office action dated October 28, 2019, please consider Applicant's amendments and remarks, as shown below.

Amendments to the Specification: none.

Amendments to the Claims begin at page 2 of this paper.

Amendments to the Drawings: none.

Remarks begin at page 6 of this paper.

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AMENDMENTS TO THE CLAIMS

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

1. **(Previously presented)** 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 at a concentration of 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.**(Previously presented)** 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.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

26.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

27.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

28.**(Previously presented)** 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 ±0.5; and

purified water, q.s. to 100 weight %.

REMARKS

The Office action dated October 28, 2019 and the cited references have been carefully considered.

Claims 1, 4, 6-12, and 24-28 are currently pending. No new matter has been added. Reconsideration of the application is respectfully requested.

Status of the Claim

Claims 1, 4, 6-12, and 24-28 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 2016205001 and Donello (US 2012/0328670).

Claims 1, 4, 6-12, and 24-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of Application No. 15/977088.

Claims 1, 4, 6-12, and 24-28 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 13-40 of copending Application No. 16/179,561.

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

Rejection of claims 1, 4, 6-12, and 24-28 under 35 U.S.C. § 103 as being unpatentable over WO 2016205001 and Donello (US 2012/0328670)

Applicant respectfully traverses this rejection because WO 2016205001 is not an effective prior art reference against the claims of the present invention, and as Donello does not teach or suggest all of the limitations of independent claims 1 and 28.

Regarding WO 2016205001, this PCT publication corresponds in disclosure to that of US application 15/173,961, of which the instant application is a continuation-in-part, and which was filed on the same date (June 6, 2016) as WO 2016/205001. Each of WO2016205001 and US 15/173,961 further claim the benefit of prior filed provisional application 62/181,481. As the composition claimed in the present application is fully supported by the same disclosure in US 15/173,961 as in the corresponding disclosure of WO2016205001 as noted by the Examiner, the present claimed composition is entitled to the same priority dates as cited WO2016205001, and cited WO2016205001 is accordingly not an effective prior art reference against the present claims.

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Regarding Donello, to demonstrate that a claim is obvious, the party asserting invalidity must present evidence that all limitations of the claim are taught or suggested 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 Donello is there teaching or suggestion of a tazarotene oil-in-water emulsion having a tazarotene concentration of 0.045%, as recited in independent claim 1, or a composition having a tazarotene concentration of 0.045% and consisting essentially of the further components as recited in independent claim 28. To the contrary, Donello teaches compositions of particles comprising biodegradable polymer and a retinoid (which may be tazarotene). Thus, Donello does not teach or suggest all of the limitations of independent claims 1 and 28. Further, as Donello is specifically directed towards compositions comprising particles of biodegradable polymer and a retinoid, it would go against the teachings of Donello to modify the disclosed compositions to be in the form of an oil in water emulsion as claimed in present claim 1, and to consist essentially of the corresponding disclosed components thereof as claimed in present claim 28, rather than polymer particles comprising the retinoid. Consequently, these claims are clearly nonobvious over Donello.

Rejection of claims 1, 4, 6-12, and 24-28 on the ground of nonstatutory double patenting

Claims 1, 4, 6-12, and 24-28 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of Application No. 15/977088. As Appl. No. 15/977088 is now abandoned, this provisional rejection is now moot.

Rejection of claims 1, 4, 6-12, and 24-28 under 35 U.S.C. § 101 over copending Application No. 16/179,561

Claims 1, 4, 6-12, and 24-28 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 13-40 of copending Application No. 16/179,561. Reconsideration of this rejection under 35 U.S.C. § 101 is respectfully urged, as the present

application claims and those of Appl. No. 16/179,561 are not directed towards the same invention, as rather the instant claims are directed towards a specified composition, while those of Appl. No. 16/179,561 are directed towards a method of treating acne vulgaris. Accordingly this rejection under 35 U.S.C. § 101 is in clear error.

If the Examiner intends to modify this rejection to be a nonstatutory obviousness type provisional double patenting rejection, 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, as no claims have yet been indicated as otherwise being allowable.

Conclusion

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

Electronic Acknowledgement Receipt	
EFS ID:	38422305
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:	99336.000342
Receipt Date:	28-JAN-2020
Filing Date:	02-NOV-2018
Time Stamp:	15:56:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		P05877_2_CIP1_US_Response_JAN_2020.pdf	168843 ca0104596ad7e618b1dfc92b2a82a120f4ba8ae	yes	8

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	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	8
Warnings:			
Information:			
	Total Files Size (in bytes):	168843	

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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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Angel Arturo	99336.000342	1093

134756 7590 10/28/2019

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

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
10/28/2019	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

Office Action Summary	Application No. 16/179,576	Applicant(s) Arturo et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1621	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/19/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,4,6-12 and 24-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,4,6-12 and 24-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 7/19/2019.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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, 4, 6-12, 24-28 is pending.

Applicants response filed 7/19/2019 has been received and entered in the application.

Action Summary

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) is withdrawn due to applicants amendment of claims.

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)) is withdrawn due to applicants amendment of claims.

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) is withdrawn due to applicants amendment of claims.

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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) is maintained for claims 1, 4, 6-12.

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).

Response to Arguments

Applicant's arguments with respect to claims 1, 4, 6-12 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection.

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, 4, 6-12 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over WO 2016205001 (WO 001) of record as disclosed in the IDS dated (7/19/2019) and Donello (U.S. Publication 2012/0328670).

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Dow teaches topical pharmaceutical compositions comprising a combination of active ingredients, and methods using the same, for treating psoriasis (para 0002). Dow teaches a composition comprising halobetasol (a corticosteroid) and tazarotene (a retinoid) is synergistically more efficacious than the combined efficacies (i.e., the sum of the efficacies) of compositions, each comprising only one of these active ingredients (pargra 0020). Dow teaches that the retinoid is present at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or tazarotenic acid salt is included in a composition of the present invention at a positive concentration less than 0.05 wt%. (para 0032). Dow teaches the retinoid is present in the composition at a concentration in the range from about 0.001 to about 0.09 wt%, or from about 0.001 to about 0.08 wt%, or from about 0.001 to about 0.07 wt%, or from about 0.001 to about 0.06 wt%, or from about 0.01 to about 0.09 wt%, or from about 0.01 to about 0.08 wt%, or from about 0.01 to about 0.07 wt%, or from about 0.01 to about 0.06 wt%, or from about 0.001 to about 0.049 wt%, or from about 0.005 to about 0.045 wt%, or from about 0.005 to about 0.04 wt%, or from about 0.005 to about 0.03 wt%, or from about 0.005 to about 0.02 wt%, or from about 0.005 to about 0.01 wt%, or 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%.(para 0033). Dow teaches that a topical pharmaceutical composition of the present invention is in the dosage form of gel, emulsion (including **lotion,** cream, and milk), shampoo, foam, suspension, liquid, spray, paste or ointment. In certain preferred embodiments, a topical pharmaceutical composition of the present invention is **an oil-in-water emulsion**, in which an internal

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oil phase is dispersed in a continuous aqueous phase. Alternatively, water-in-oil-in-water, water-in-oil and oil-in-water-in-oil emulsions are also contemplated. The emulsion may be a macroemulsion, a microemulsion, or a nanoemulsion. Also contemplated are other formulations in which an oil phase and a water phase coexist within the formulation, such as a multivesicular emulsion, which is not a true emulsion. Also contemplated is a liposomal dispersion in a gel, cream or other dosage form. Also contemplated are other formulations in which non-polar and polar liquid ingredients, with or without semipolar ingredients, coexist with the formulation (paragraph 0038).

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Ingredient	Function	Concentration (wt%)			
		Range 1	Range 2	Range 3	Preferred embodiment
Halobetasol propionate	Class 1 Corticosteroid	0.001-0.04	0.005-0.03	0.005-0.02	0.01
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

(table 2 with specific amounts in table 4 (which are the same amounts as disclosed in instant claim 40)). Dow teaches in table 8-9 the topical administration up to 12 weeks.

Dow does not teach acne.

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Donello teaches a composition of only (emphasis added) tazarotenic acid or a pharmaceutically acceptable salt, ester or amid thereof (claim 10). Donello teaches the treatment of skin disorders such as acne vulgaris with the administration of tazarotenic acid (claim 11-12).

It would have been obvious to employ tazarotenic acid as the sole agent in the treatment of acne in view of Dow. One would have been motivated to employ tazarotenic acide because it is known that topically administered tazarotenic acid is effective in the treatment of skin disorders (e.g. psoriasis and acne) as disclosed by both Dow and Donello with a reasonable expectation of success absence evidence to the contrary.

With regards the limitation "wherein the tazarotene or tazarotenic acid salt is dissolved in a liquid oil component of the emulsion", since it is known in the art that the composition is in an oil-in-water emulsion as disclose by Dow, it would have been obvious that in order to obtain the oil-in-water emulsion, the active agent would have been dissolved in an oil. Furthermore, the instant claims are drawn to a method of treating acne not a method of preparing said composition.

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

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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(l)(1) - 706.02(l)(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

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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 1-4, 6-12, 24-28 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. 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.

New Rejection

Claims 1-4, 6-12, 24-28 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims of 13-40 copending Application No. 16/179,561 (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 '561 application recite a composition (tazarotene) for the treatment of acne (e.g. skin disease). 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.

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

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Claims 1-4, 6-12, 24-28 is rejected.

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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

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Notice of References Cited	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	US-20120328670-A1	12-2012	Donello; John E.	A61K9/0014	424/400
	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	
	V	
	W	
	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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Arturo et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	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
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc

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

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16179576
Filing Date	2018-11-02
First Named Inventor	Arturo, Angel
Art Unit	1621
Examiner Name	Cruz, Kathrien A.
Attorney Docket Number	99336.000342

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6730308	B1	2004-05-04	Sefton	
	2	8808716	B2	2014-08-19	Loupenok	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120129824	A1	2012-05-24	Angel et al.	
	2	20140349981	A1	2014-11-27	Evers et al.	
	3	20160367570	A1	2016-12-22	Dow et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16179576
	Filing Date	2018-11-02
	First Named Inventor	Arturo, Angel
	Art Unit	1621
	Examiner Name	Cruz, Kathrien A.
	Attorney Docket Number	99336.000342

	1	2016/205001	WO	A1	2016-12-22	Dow et al.		
	2	1528328	CN	A	2004-09-15	Zheng et al.		☒
	3	2012/087443	WO	A1	2012-06-28	Angel et al.		☐
	4	2461/MUM/2009	IN		2012-03-30	Ghandi		☒
	5	2012/061630	WO	A2	2012-05-10	Jackson		☐
	6	0047211	WO		2000-08-17	Bershad et al.		☐
	7	2004/058262	WO	A1	2004-07-15	Saoji et al.		☐
	8	2012/051614	WO	A2	2012-04-19	Kulesza et al.		☐
	9	1528313	CN	A	2004-09-15	Li		☒

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NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A.C/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16179576
	Filing Date	2018-11-02
	First Named Inventor	Arturo, Angel
	Art Unit	1621
	Examiner Name	Cruz, Kathrien A.
	Attorney Docket Number	99336.000342

	1	International Search Report and Written Opinion of PCT/US18/32359 of the International Searching Authority completed 17 July 2018 (10 pages).	
	2	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, July 2009, Vol. 8, no. 7, pages 650-654.	
	3	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, June 1999,Vol. 63, no. 6, pages 349-354.	
	4	Lebwohl 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, pages 64-66 (XP009191230).	
	5	Dhawan et al.: "Tazarotene cream (0.1%) in combination with betamethasone valerate foam (0.12%) for plaque-type psoriasis", Journal of Drugs in Dermatology, New York NY, vol. 4, no. 2, 1 March 2005, pages 228-230 (XP009159245).	
	6	Tazorac® Brochure (ALLERGAN packaging insert, revised July/2017, 13 pages).	
	7	International Search Report and Written Opinion of PCT/US16/035991 of the International Searching Authority completed 6 August 2016 (10 pages).	
	8	Hecker et al., In vitro compatibility of tazarotene with other topical treatments of psoriasis, pp 1008-1011, June 2000, Elsevier, US.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/KATHRIEN A CRUZ/	Date Considered	10/23/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A.C/

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Padagis Ex. 1029
IPR Petition - USP 11,311,482

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16179576
	Filing Date	2018-11-02
	First Named Inventor	Arturo, Angel
	Art Unit	1621
	Examiner Name	Cruz, Kathrien A.
	Attorney Docket Number	99336.000342

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Andrew J. Anderson/	Date (YYYY-MM-DD)	2019-07-19
Name/Print	Andrew J. Anderson	Registration Number	33564

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour to complete, including gathering, preparing and submitting the completed application 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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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 record s.

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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.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	"2013205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:24
L2	13	"6730308"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:24
L3	11	"8808716"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:26
L4	2	"20130205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:41
L5	3	"2013205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:42
L6	4	"2016205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:44
L7	2	"20160205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:44
L8	4	"2016205001"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 12:44
L9	8	"2016205001"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 12:47
L10	31	"8808716"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L11	17	"10251895"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L12	5	"20120129824"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L13	2	"20140349981"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L14	3	"20160367570"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32

L15	8	"2016205001"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L16	39	"1528238"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L17	12	"2012087443"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:32
L18	3	((("ARTURO") near3 ("Angel")) and (("PILLAI") near3 ("Radhakrishnan"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 13:33
L19	3	L18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:33
L20	9520	tazarotene	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 13:33
L21	3400	L20 and acne	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 13:33
L22	2707	L21 and @py<"2017"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 13:33
L23	556	L22 and "acne vulgaris"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/23 13:33
L24	556	L23	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/10/23 13:33

10/23/2019 1:34:38 PM
C:\Users\kcruz\Documents\EAST\Workspaces\16179561.wsp

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	07/19/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 23	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CHRISTINE V MOORE/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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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Padagis Ex. 1029
IPR Petition - USP 11,311,482

Confirmation No.: 1093

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Angel Arturo
Applicant:	Valeant Pharmaceuticals North America
Application No.:	16/179,576
Filed:	November 2, 2018
Examiner:	CRUZ, Kathrien Ann
Group/Art Unit:	1621
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

AMENDMENT AND RESPONSE TO OFFICE ACTION UNDER 37 C.F.R § 1.111

Dear Sir:

In response to the Office action dated March 20, 2019, please consider Applicant's amendments and remarks, as shown below.

Amendments to the Specification: none.

Amendments to the Claims begin at page 2 of this paper.

Amendments to the Drawings: none.

Remarks begin at page 6 of this paper.

This Response is filed with a petition for a one-month extension of time. Should the undersigned representative be mistaken as to time or fee, please charge Deposit Account No. 03-3875 of Harter Secrest & Emery LLP for any required fees.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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Filing Date	2018-11-02
First Named Inventor	Arturo, Angel
Art Unit	1621
Examiner Name	Cruz, Kathrien A.
Attorney Docket Number	99336.000342

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6730308	B1	2004-05-04	Sefton	
	2	8808716	B2	2014-08-19	Loupenok	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120129824	A1	2012-05-24	Angel et al.	
	2	20140349981	A1	2014-11-27	Evers et al.	
	3	20160367570	A1	2016-12-22	Dow et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

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	Attorney Docket Number	99336.000342

	1	2016/205001	WO	A1	2016-12-22	Dow et al.		
	2	1528328	CN	A	2004-09-15	Zheng et al.		X
	3	2012/087443	WO	A1	2012-06-28	Angel et al.		☐
	4	2461/MUM/2009	IN		2012-03-30	Ghandi		☒
	5	2012/061630	WO	A2	2012-05-10	Jackson		☐
	6	0047211	WO		2000-08-17	Bershad et al.		☐
	7	2004/058262	WO	A1	2004-07-15	Saoji et al.		☐
	8	2012/051614	WO	A2	2012-04-19	Kulesza et al.		☐
	9	1528313	CN	A	2004-09-15	Li		☒

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NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5

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	1	International Search Report and Written Opinion of PCT/US18/32359 of the International Searching Authority completed 17 July 2018 (10 pages).	
	2	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, July 2009, Vol. 8, no. 7, pages 650-654.	
	3	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, June 1999,Vol. 63, no. 6, pages 349-354.	
	4	Lebwohl 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, pages 64-66 (XP009191230).	
	5	Dhawan et al.: "Tazarotene cream (0.1%) in combination with betamethasone valerate foam (0.12%) for plaque-type psoriasis", Journal of Drugs in Dermatology, New York NY, vol. 4, no. 2, 1 March 2005, pages 228-230 (XP009159245).	
	6	Tazorac® Brochure (ALLERGAN packaging insert, revised July/2017, 13 pages).	
	7	International Search Report and Written Opinion of PCT/US16/035991 of the International Searching Authority completed 6 August 2016 (10 pages).	
	8	Hecker et al., In vitro compatibility of tazarotene with other topical treatments of psoriasis, pp 1008-1011, June 2000, Elsevier, US.	

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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Signature	/Andrew J. Anderson/	Date (YYYY-MM-DD)	2019-07-19
Name/Print	Andrew J. Anderson	Registration Number	33564

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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.

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(54) **Title**: TOPICAL COMPOSITIONS COMPRISING A CORTICOSTEROID AND A RETINOID FOR TREATING PSORIASIS

(57) **Abstract**: Topical pharmaceutical compositions comprise a combination of a corticosteriod a retinoid; and methods for treating psoriasis with same.

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TOPICAL COMPOSITIONS COMPRISING A CORTICOSTEROID AND A RETINOID FOR TREATING PSORIASIS

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to United States Provisional Patent Application Serial number 62/181,481, filed on June 18, 2015, the content of which is relied upon and incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to topical compositions and methods for treating psoriasis. In particular, this invention relates to topical pharmaceutical compositions comprising a combination of active ingredients, and methods using the same, for treating psoriasis. More particularly, this invention relates to topical pharmaceutical compositions comprising a combination of a corticosteroid and a retinoid, and methods using the same, for treating psoriasis.

[0003] Psoriasis is a chronic skin disease affecting approximately about 2 – 4 percent of the population world-wide. Over seven million people in the United States are affected. While the pathogenesis of psoriasis has not yet been fully elucidated, significant evidence indicates that epidermal changes occur as a secondary response to cellular immune infiltrates in the skin. Psoriasis is characterized by discrete areas of skin inflammation with redness, thickening, intense scaling, and in some cases, itching. The disease has significant impact on the quality of life of affected individuals, both physically and psychologically.

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Today there is no cure for psoriasis, and treatment is directed at reducing the severity and extent of the psoriatic plaques and the related symptoms. The primary measurement of treatment success used by the U.S. Food and Drug Administration in evaluating products for the treatment of psoriasis is significant overall improvement in psoriasis severity based on Investigators Global Assessment.

[0004] Systemic therapy such as methotrexate, or biologics such as etanercept, adalimumab, infliximab, etc. are the preferred treatment when the skin involvement is extensive; e.g., ten percent of the body surface area or more. A large number of those suffering from psoriasis have less extensive disease, and topical medications are considered a safer and more prudent alternative in most of these cases. Among the topical therapies are anti-inflammatory corticosteroids; particularly, the super potent ones such as halobetasol propionate, vitamin D derivatives, such as calcipotriene, a retinoid known as tazarotene, and coal tar. Each of the topical therapies has some degree of effectiveness, but each has limitations in the degree of improvement of the psoriatic plaques that can be achieved or the occurrence of adverse effects.

[0005] Halobetasol propionate (a topical corticosteroid) is commercially available and has been used to treat psoriasis for about 20 years or more at strength of 0.05% in a variety of dosage forms such as creams and ointments. Halobetasol is quite effective in improving the signs and symptoms of psoriasis; however both local and systemic adverse effects limit its chronic use. Treatment duration is limited to 2 weeks by FDA, and signs and symptoms of psoriasis often rebound (worsen) following the end of treatment.

[0006] For many years tazarotene (a retinoid) has been commercially available and has been used to treat psoriasis topically as creams and gels of 0.05% and 0.1%. Tazarotene generally shows moderate effectiveness in psoriasis; however its use in psoriasis is severely limited by local skin irritation. Dermatologists treated psoriasis and achieved good clinical results using sequential therapy with a corticosteroid in the morning and tazarotene applied in the evening.

[0007] The need still exists for more effective and safer topical medicaments with reduced adverse effects for the management of psoriasis.

SUMMARY OF THE INVENTION

[0008] In general, the present invention provides topical compositions and methods for treating psoriasis.

[0009] In one aspect, the present invention provides topical pharmaceutical compositions comprising a combination of active ingredients selected from the group consisting of dermatological immune response-modulating agents and anti-proliferative agents, and methods using the same, for treating psoriasis.

[0010] In another aspect, the present invention provides topical pharmaceutical compositions comprising a combination of: (a) a corticosteroid or a pharmaceutically acceptable salt or ester thereof; and (b) a retinoid or a pharmaceutically acceptable salt or ester thereof, and methods using the same, for treating psoriasis. In one embodiment, such psoriasis is plaque psoriasis.

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[0011] In still another aspect, the present invention relates to topical pharmaceutical compositions comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt, and methods using the same, for treating psoriasis. In one embodiment, such psoriasis is plaque psoriasis.

[0012] In yet another aspect, the present invention provides topical pharmaceutical compositions comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt or a pharmaceutically acceptable non-ethyl ester of tazarotenic acid, and methods using the same, for treating psoriasis; wherein each of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt or a pharmaceutically acceptable non-ethyl ester of tazarotenic acid is present in the composition at a positive concentration of less than 0.09% based on the weight of the composition. A non-ethyl ester of tazarotenic acid is an ester of tazarotenic acid that is not the ethyl ester. For example, a non-ethyl ester can be methyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, aryl, phenyl, or naphthyl ester. In one embodiment, the concentration of halobetasol or a pharmaceutically acceptable salt is in the range from about 0.001 to about 0.049 weight percent ("wt %"); and the concentration of tazarotene or a pharmaceutically acceptable tazarotenic acid salt is in the range from about 0.001 to about 0.049 wt %.

[0013] Other features and advantages of the present invention will become apparent from the accompanying drawings and the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[0014] In general, the present invention provides topical compositions and methods for treating psoriasis.

[0015] Throughout this disclosure, unless otherwise indicated, the concentration of an ingredient of the composition is in percent by weight of the total composition.

[0016] In one aspect, the present invention provides topical pharmaceutical compositions comprising a combination of active ingredients selected from the group consisting of dermatological immune response-modulating agents and anti-proliferative agents, and methods using the same, for treating psoriasis.

[0017] In another aspect, a topical pharmaceutical composition of the present invention is used to treat or ameliorate psoriasis in patients suffering from moderate to severe plaque psoriasis.

[0018] In yet another aspect, a topical pharmaceutical composition of the present invention is used to treat or ameliorate psoriasis in patients with psoriasis covering up to about 12 percent of the body surface area.

[0019] The inventors have unexpectedly discovered that a topical dermatological composition comprising two different active ingredients selected from the group consisting of dermatological immune response-modulating agents and anti-proliferative agents is synergistically more efficacious than the combined efficacies of compositions, each comprising only one of the active ingredients in

the treatment of psoriasis. In one aspect, one active ingredient is a corticosteroid, and the other active ingredient is a retinoid. Corticosteroids are also known alternatively as steroids, corticoids or glucocorticosteroids.

[0020] In particular, the inventors surprisingly discovered that a composition comprising halobetasol (a corticosteroid) and tazarotene (a retinoid) is synergistically more efficacious than the combined efficacies (i.e., the sum of the efficacies) of compositions, each comprising only one of these active ingredients.

[0021] In another aspect, the present invention provides topical pharmaceutical compositions comprising a combination of: (a) a corticosteroid or a pharmaceutically acceptable salt or ester thereof; and (b) a retinoid or a pharmaceutically acceptable salt or ester thereof, and methods using the same, for treating psoriasis.

[0022] In one aspect, a corticosteroid included in a composition of the present invention is selected from the corticosteroids of class 1. The classification of corticosteroids and examples thereof are disclosed in Table 1.

Table 1

Class 1 – Superpotent Topical Corticosteroids
Clobetasol propionate Betamethasone dipropionate Halobetasol propionate Fluocinonide Diflorasone diacetate

[0023] Clobetasol propionate and halobetasol propionate have been used for treating steroid responsive dermatoses, including psoriasis, always at a concentration of 0.05%, in various dosage forms including ointments, creams, solutions, sprays, and gels.

[0024] Betamethasone dipropionate has been used for treating steroid responsive dermatoses, including psoriasis, always at a concentration of 0.064% equivalent to 0.05% betamethasone, in several dosage forms including ointments, creams, gels and lotions.

[0025] Fluocinonide has been used for treating steroid responsive dermatoses, including psoriasis, at various concentrations ranging from 0.001% to 0.1%, in various dosage forms including ointments, creams, gels and solutions. Only the 0.1% formulations have been classified as superpotent.

[0026] Diflorasone diacetate has been used for treating steroid responsive dermatoses, including psoriasis, at various concentration of 0.05%, as an ointment and as a cream. Only ointment formulation has been classified as superpotent.

[0027] HPA axis suppression from long term use topical preparations containing clobetasol propionate and halobetasol propionate and other super potent corticosteroids has limited the duration of therapy allowed by FDA. The duration on therapy allowed in the labeling for super potent topical corticosteroids is normally limited to two weeks.

[0028] In one aspect, the corticosteroid is present at a concentration below that which is presently utilized in topical formulations. The formulation contains the corticosteroid at a positive concentration less than 0.05% w/w.

[0029] In certain embodiments of the present invention, a corticosteroid or a pharmaceutically acceptable salt or ester thereof is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition. Alternatively, the corticosteroid is present in the composition at a concentration in the range from about 0.001 to about 0.049 wt%, or from about 0.005 to about 0.04 wt%, or from about 0.005 to about 0.035 wt%, or from about 0.005 to about 0.03 wt%, or from about 0.005 to about 0.025 wt%, or from about 0.005 to about 0.015 wt%, or from about 0.005 to about 0.01 wt%.

[0030] In still another aspect, a retinoid included in a composition of the present invention is selected from the group consisting of tazarotene, bexarotene, and adapalene. These retinoids are commonly known as third-generation retinoids.

[0031] In yet another aspect, a retinoid belonging to the group known as second-generation retinoids (such as etretinate and acitretin) may be used in a composition of the present invention for patients who suffer from the psoriatic condition.

[0032] In one aspect, the retinoid is present at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or

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tazarotenic acid salt is included in a composition of the present invention at a positive concentration less than 0.05 wt%.

[0033] In certain embodiments of the present invention, a retinoid or a pharmaceutically acceptable salt or ester thereof is present in the composition at a positive concentration of less than 0.09% based on the weight of the composition. For example, the retinoid is present in the composition at a concentration in the range from about 0.001 to about 0.09 wt%, or from about 0.001 to about 0.08 wt%, or from about 0.001 to about 0.07 wt%, or from about 0.001 to about 0.06 wt%, or from about 0.01 to about 0.09 wt%, or from about 0.01 to about 0.08 wt%, or from about 0.01 to about 0.07 wt%, or from about 0.01 to about 0.06 wt%, or from about 0.001 to about 0.049 wt%, or from about 0.005 to about 0.045 wt%, or from about 0.005 to about 0.04 wt%, or from about 0.005 to about 0.03 wt%, or from about 0.005 to about 0.02 wt%, or from about 0.005 to about 0.01 wt%, or 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%.

[0034] In another aspect, the pharmaceutical composition comprises a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt or a pharmaceutically acceptable non-ethyl ester of tazarotenic acid, for treating psoriasis; wherein (a) halobetasol or a pharmaceutically acceptable salt or ester thereof is present in the composition at a concentration in the range from about 0.005 to about 0.035 wt%, or from about 0.005 to about 0.025 wt%, or from about 0.01 to about 0.025 wt%; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt or a pharmaceutically acceptable non-ethyl ester

of tazarotenic acid is present in the composition at a concentration in the range from about 0.001 to about 0.049 wt%, or 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 0.04 wt%, or from about 0.02 to about 0.045 wt%, or from about 0.03 to about 0.045 wt%.

[0035] In still another aspect, the pharmaceutical composition comprises a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof at a concentration of 0.01 wt%; and (b) tazarotene at a concentration of 0.045 wt%, or a pharmaceutically acceptable tazarotenic acid salt at a concentration that provides 0.045 wt% as tazarotene, for treating psoriasis.

[0036] In still another aspect, the pharmaceutical composition comprises a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof at a concentration of 0.01 wt%; and (b) tazarotene at a concentration of 0.045 wt%, or a pharmaceutically acceptable ester, other than ethyl ester, of tazarotenic acid at a concentration that provides 0.045 wt% as tazarotene, for treating psoriasis. Non-limiting examples of non-ethyl esters of tazarotenic acid are disclosed herein above.

[0037] In yet another aspect, the pharmaceutical composition comprises a combination of: (a) halobetasol propionate at a concentration of 0.01 wt%; and (b) tazarotene at a concentration of 0.045 wt%, for treating psoriasis.

[0038] In one aspect, a topical pharmaceutical composition of the present invention is in the dosage form of gel, emulsion (including lotion, cream, and milk), shampoo, foam, suspension, liquid, spray, paste or ointment. In certain preferred

embodiments, a topical pharmaceutical composition of the present invention is an oil-in-water emulsion, in which an internal oil phase is dispersed in a continuous aqueous phase. Alternatively, water-in-oil-in-water, water-in-oil and oil-in-water-in-oil emulsions are also contemplated. The emulsion may be a macroemulsion, a microemulsion, or a nanoemulsion. Also contemplated are other formulations in which an oil phase and a water phase coexist within the formulation, such as a multivesicular emulsion, which is not a true emulsion, disclosed in Espinoza, U.S. Patent No. 6,709,663. Also contemplated is a liposomal dispersion in a gel, cream or other dosage form. Also contemplated are other formulations in which non-polar and polar liquid ingredients, with or without semipolar ingredients, coexist with the formulation.

[0039] In addition to the active ingredients as disclosed above, a composition of the present invention comprises 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.

[0040] The formulation of the invention may desirably contain a thickening agent to provide viscosity so that the formulation may be provided in the form of a lotion, gel, cream, or ointment. Preferably, but not necessarily, the thickening agent is 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.

[0041] 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 C_{10}-C_{30} 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.

[0042] A surfactant or emulsifier is 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 CH_3–$(CH_2)_{10–16}$–$(O$-$C_2H_4)_{1–25}$–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).

[0043] 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 (C_{10}-C_{30}) alkyl acrylates, and crosslinked with allylpentaerythritol.

[0044] 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.

[0045] 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 its salts may be included in a formulation of the present invention.

[0046] 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;

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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).

[0047] 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.

[0048] 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.

[0049] 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.

[0050] A DCAE that is suitable for the present invention has the formula $R_1OOC\text{-}(CH_2)_n\text{-}COOR_2$, 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 $CH_3CH_2OOC\text{-}(CH_2)_8\text{-}COOCH_2CH_3$. 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.

[0051] 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 CH_3-$(CH_2)_n$-$COOR_1$, wherein R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and wherein $(CH_2)_n$ 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.

[0052] The liquid oil phase may beneficially be used to dissolve one or more of the active ingredients within the emulsion or other type of formulation of the present invention. In one embodiment the corticosteroid and the retinoid are both dissolved in the liquid oil phase within the formulation at room temperature. In another embodiment the corticosteroid is dissolved in the liquid oil phase and the retinoid is suspended within the formulation at room temperature. In yet another embodiment the retinoid is dissolved in the liquid oil phase and the corticosteroid is suspended within the formulation at room temperature. In the case wherein the retinoid or the corticosteroid is suspended in the formulation, it is preferred that the

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suspended active ingredient be micronized, namely that the mean particle size is preferably about 25 microns in diameter or less.

[0053] In one aspect, a composition of the present invention comprises the ingredients at the concentrations shown in Table 2.

Table 2

Compositions of the Present Invention for Treating Psoriasis

Ingredient	Concentration (wt%)		
	Range 1	Range 2	Range 3
Class-1 Corticosteroid	0.001-0.049	0.005-0.035	0.01-0.025
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	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

[0054] Non-limiting examples of compositions of the present invention are shown in Table 3.

Table 3

Some Emulsion Compositions of the Present Invention for Treating Psoriasis

Ingredient	Function	Concentration (wt%)			
		Range 1	Range 2	Range 3	Preferred embodiment
Halobetasol propionate	Class 1 Corticosteroid	0.001-0.04	0.005-0.03	0.005-0.02	0.01
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.

[0055] A lotion having a composition as shown in the last column of Table 2 was prepared as follows.

[0056] A separate aqueous phase was made. In a manufacturing vessel equipped with a mixing implement (such as a propeller) and temperature control,

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

[0057] A separate oil phase was made. In a vessel equipped with a mixing implement such as a propeller, diethyl sebacate, halobetasol propionate, and tazarotene were combined. The mixture was agitated until a solution was achieved. With continuous mixing, light mineral oil and sorbitan monooleate were added. Mixing is continued until a solution is obtained.

[0058] In a separate vessel, a 1N solution of sodium hydroxide is prepared.

[0059] With high speed mixing, the oil phase containing the active ingredients (halobetasol propionate and tazarotene) was added to the aqueous phase. Pemulen™ TR-1 was slowly added into the mixture. Mixing was continued until a homogeneous emulsion was obtained. Mixing speed was 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 was added incrementally to obtain a pH of 5.5 ± 0.5. Mixing continued further until a homogeneous lotion was obtained, such as for 30 minutes to 3 hours.

[0060] Alternatively, Pemulen^{TM} TR-1 may be added into the aqueous phase when it was made.

[0061] A clinical study in psoriasis patients was conducted to compare the efficacy of a composition of the present invention containing halobetasol propionate and tazarotene ("IDP-118"); placebo ("Vehicle"); a composition containing only halobetasol propionate ("HP"); and a composition containing only tazarotene ("Taz"). The compositions for the clinical studies are shown in Table 4.

Table 4

Compositions for Clinical Studies

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta-sol propio-nate only	Tazaro-tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen™ TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	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	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

[0062] A double blind clinical study was conducted whereby neither the psoriasis patient nor the investigator knew the identity of the test lotion assigned. The blindly labeled lotions were applied to the psoriasis plaques once daily. All test lotions were the same except for the differences is in active ingredients being

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studied. Approximately 212 subjects were randomized in a 2:2:2:1 ratio to receive IDP-118 (a composition of the present invention, comprising halobetasol propionate 0.01% and tazarotene 0.045%) Lotion, HP (halobetasol propionate 0.01%) Lotion, Taz Lotion (tazarotene 0.045%), and Lotion Vehicle (no active ingredients), as follows:

- 59 subjects to IDP-118 Lotion ("IDP 118 group")
- 63 subjects to HP 0.01% Lotion ("HP group")
- 59 subjects to Taz 0.045% Lotion ("Taz group")
- 31 subjects to Lotion Vehicle ("Vehicle group").

Eighteen investigative centers participated in the clinical study, each following the same protocol.

The key enrollment criteria were that each subject had at least moderate severity of psoriasis; i.e., a score of 3 or 4, as defined by the Investigator Global Assessment ("IGA") scale shown in Table 5.

Table 5

Investigator's Global Assessment

Score	Grade	Description
0	Clear	No evidence of scaling No evidence of erythema No evidence of plaque elevation above normal skin level
1	Almost clear	Some plaques with fine scales Faint pink/light red erythema on most plaques Slight or barely perceptible elevation of plaques above normal skin level
2	Mild	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale Most to all plaques are pink/light red to bright red in color Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
3	Moderate	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or course scale; Most to all plaques are bright red, some plaque may be dark red in color Definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
4	Severe	Most to all plaques are covered with coarse, thick scales Most or all plaques are bright, dark or dusky red Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

[0063] For each patient the investigator determined and recorded the treatable areas affected by psoriasis at the Baseline visit. Treatable areas were defined as all areas of psoriasis identified at Baseline comprising a body surface area (BSA) of 3% to 12% and designated for treatment with study drug. According to protocol the treatable affected areas did not include the face, scalp, palms, soles, axillae, or intertriginous areas. If palms and soles were affected, study drug could be applied at the discretion of the investigator; however, these areas were not included in the

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treatable BSA or efficacy assessments. Also a target lesion (psoriasis plaque) was identified and at the Baseline visit to be used solely for assessment of three signs of psoriasis: erythema, plaque elevation, and scaling.

[0064] The assigned study drug was applied topically to the affected area (as determined by the investigator at Baseline) once daily for 8 weeks. The initial application was made at the investigational center during the day as per instruction from the study coordinator or designee. The subjects were instructed to avoid exposure to direct sunlight to prevent sunburn. Subjects applied their daily treatments at home as explained by the study coordinator or designee at each investigational center. The subjects were asked to return their used containers of study drug at their clinic visits on Weeks 2, 4, 6, and 8. Subjects were asked to not apply study drug on the day of a clinic visit until after assessments were completed at the clinic. The study coordinator or designee at each investigational center dispensed 2 new containers of study drug to each subject at Baseline and Weeks 2, 4, and 6. Upon completion of the 8-week treatment period all study drug supplies were turned-in to the investigational center, and all subjects were asked to return to the investigational center 4 weeks later for a post-treatment cessation follow-up visit (Week 12). During the study, each subject was only permitted to use approved non-medicated cleansers and moisturizers; no sunscreens or other skin care products were permitted on the treatment areas.

[0065] The investigator monitored the efficacy at each study visit by assessing the treatable area and determining the IGA score for psoriasis severity, and grading the target lesion for erythema, plaque elevation, and scaling in each subject.

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[0066] Information on reported and observed adverse events ("AEs") was obtained at each visit. An abbreviated physical examination was performed at Baseline, Week 8 (end of treatment), and Week 12 (the 4-week post-treatment cessation follow-up visit) for all subjects.

[0067] The signs of psoriasis (erythema, plaque elevation, and scaling) were assessed for the selected target lesion using the grading scales displayed in Table 4. Improvements in these signs are a measure of the efficacy of a studied drug. Efficacy assessment was made at 2, 4, 6, and 8 weeks during the treatment phase and at the 12-week visit (the 4-week post treatment follow-up visit).

[0068] Tolerability was evaluated through assessments of selected local signs and symptoms (itching, dryness, and burning/stinging). In addition, the treatment areas were examined by the evaluator at each visit for presence or absence of significant known drug-related adverse events: skin atrophy, striae, telangiectasia, and folliculitis.

[0069] Efficacy of the four study drugs was assessed based on the IGA scores, that is improvement in the IGA psoriasis severity score over time.

[0070] Clinical Efficacy was determined based on the percentage of subjects who were treatment successes.

[0071] The IDP-118 group was compared to each of the other treatment groups: (1) HP group, (2) Taz group, and (3) Vehicle group.

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[0072] To be judged as a treatment success, subjects had to show two-grade improvement in IGA from the baseline, and to have an IGA score of "clear, or almost clear" at the evaluation time. Subjects not achieving treatment success by this standard were considered treatment failures, even though such subjects may have experienced some degree of improvement in their psoriasis.

[0073] Results

[0074] The efficacy of IDP-118 comprising Halobetasol Propionate 0.01% and Tazarotene 0.045% is shown and discussed.

[0075] After completion of the clinical study the blinding codes were broken and the results tabulated. Data for dichotomized IGA with subjects categorized as Treatment Success or Failures are presented in Table 6.

[0076] As required by FDA success was defined as at least a two-grade improvement from Baseline in the IGA score and an IGA score equating to 'Clear' or 'Almost Clear'. Also shown in Table 7 is the statistical analysis of IDP-118 compared to each of the other treatment groups based on the percentage of subjects achieving Treatment Success. P-values are from a Cochran-Mantel-Haenszel test using pairwise tests comparing IDP-118 to Vehicle, IDP-118 to HP and IDP-118 to Taz. Week 12 is the follow-up evaluation time, 4 weeks after the end of treatment.

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Table 6

Treatment Successes and Failures Based on Improvement in IGA Score

Dichotomized IGA[a]	IDP-118 (N=59)	HP 0.01% (N=63)	Taz 0.045% (N=59)	Vehicle (N=31)
Week 2				
No. of Subjects	59	63	59	31
Success	7	3	1	0
Failure	52	60	58	31
p-value[b]		0.155	0.029	0.047
Week 4				
No. of Subjects	59	63	59	31
Success	15	11	1	2
Failure	44	52	58	29
p-value[b]		0.285	<0.001	0.030
Week 6				
No. of Subjects	59	63	59	31
Success	19	16	9	1
Failure	40	47	50	30
p-value[b]		0.408	0.031	0.002
Week 8				
No. of Subjects	59	63	59	31
Success	31	21	11	3
Failure	28	42	48	28
p-value[b]		0.033	<0.001	<0.001
Week 12				
No. of Subjects	55	62	47	29
Success	21	13	6	2
Failure	34	49	41	27
p-value[b]		0.042	0.004	0.002

[a] Success was defined as at least a two-grade improvement from Baseline in the IGA score and an IGA score equating to 'Clear' or 'Almost Clear'.

[b] p-value from a Cochran-Mantel-Haenszel test. Pairwise tests were conducted comparing IDP-118 to Vehicle and IDP-118 to HP or Taz.

Table 7

Percentage of Subjects Achieving Treatment Success

Duration	IDP-118	HP 0.01%	Taz 0.045%	Vehicle
Week 2	11.9	4.8	1.7	0
Week 4	25.4	17.5	1.7	6.5
Week 8	52.5	33.3	18.6	9.7
Week 12	38.2	21.0	12.8	6.9

[0077] Actual Clinical Efficacy compared to Predicted Additive Clinical Efficacy (as a percentage of subjects achieving "Treatment Success") is shown in Table 8. The "Treatment Success" percentages for the active treatment groups (IDP-118,

HP, and Taz) were corrected for vehicle effect by subtracting the actual Vehicle group results from each to determine the net Treatment Success are shown as a percentage of the number of subjects treated.

Table 8

Comparative Treatment Success Rates for IDP-118, HP, and Taz Groups

	Control-Adjusted Percentage of Patients Achieving Treatment Success During the Study			
Duration	HP Actual	Taz Actual	HP + Taz Calculated	IDP-118 Actual
Week 2	4.8	1.7	6.5	11.9
Week 4	11	-4.8	6.2	18.9
Week 8	23.6	8.9	32.5	42.8

[0078] The synergistic effect of IDP-118 is illustrated by comparing the clinical efficacy from IDP-118 to the predicted efficacy from combining HP and Taz (see Table 9). The control-adjusted percentage of patients who were successfully treated with IDP-118 was greater than the sum of control-adjusted percentages of patients who were successfully treated singly with HP and Taz at all evaluation times: 2 weeks of treatment, 4 weeks of treatment, 8 weeks of treatment, and 4 weeks after the completion of 8 weeks of treatment (Week 12).

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Table 9

Synergistic Clinical Efficacy of IDP-118 at weeks 2, 4, 8 and 12

Duration	Percent of Patients Achieving Treatment Success		Ratio of Actual to Expected
	IDP-118 Actual	HP+Taz Calculated	
Week 2	11.9	6.5	1.8
Week 4	18.9	6.2	3.0
Week 8	42.8	32.5	1.3
Week 12	31.3	20	1.6

[0079] The efficacy of IDP-118 was compared to that of HP (halobetasol propionate 0.01%), Taz (tazarotene 0.045%) and the placebo (vehicle of IDP-118) in terms of success in resolving erythema, plaque elevation, and scaling. The results are shown in Tables 10-12. The success rate for IDP-118 is higher than that of HP, and much higher than those for Taz and placebo. These comparisons were made on assessments of a target lesion that was identified at baseline before treatment was commenced.

[0080] The percentage of patients who experienced adverse events, as indicated by itching, burning, and stinging, is much lower for those who were treated with IDP-118 than those treated with HP or Taz. The results are shown in Table 13.

Table 10
Severity of Erythema Through Time

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
IDP-118						
Erythema						
Number of Subjects	59	59	59	59	59	55
0 – None	0.0%	0.0%	10.2%	6.8%	11.9%	16.4%
1 – Minimum	0.0%	23.7%	32.2%	37.3%	44.1%	32.7%
2 – Mild	6.8%	37.3%	30.5%	35.6%	28.8%	32.7%
3 – Moderate	89.8%	39.0%	25.4%	18.6%	15.3%	18.2%
4 – Severe	3.4%	0.0%	1.7%	1.7%	0.0%	0.0%
HP 0.01%						
Erythema						
Number of Subjects	63	63	63	63	63	62
0 – None	0.0%	3.2%	7.9%	12.7%	14.3%	11.3%
1 – Minimum	0.0%	12.7%	33.3%	34.9%	33.3%	29.0%
2 – Mild	7.9%	38.1%	23.8%	27.0%	33.3%	22.6%
3 – Moderate	84.1%	44.4%	34.9%	25.4%	17.5%	33.9%
4 – Severe	7.9%	1.6%	0.0%	0.0%	1.6%	3.2%

Table 10 (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Taz 0.045%						
Erythema						
Number of Subjects	59	59	59	59	59	47
0 – None	0.0%	0.0%	3.4%	1.7%	1.7%	4.3%
1 – Minimum	0.0%	5.1%	5.1%	20.3%	20.3%	25.5%
2 – Mild	8.5%	22.0%	42.4%	30.5%	32.2%	36.2%
3 – Moderate	81.4%	57.6%	37.3%	39.0%	37.3%	34.0%
4 – Severe	10.2%	15.3%	11.9%	8.5%	8.5%	0.0%
Vehicle (N=31)						
Erythema						
Number of Subjects	31	31	31	31	31	29
0 – Clear	0.0%	0.0%	3.2%	0.0%	3.2%	0.0%
1 – None	0.0%	9.7%	6.5%	16.1%	9.7%	10.3%
2 – Minimum	6.5%	25.8%	19.4%	12.9%	25.8%	34.5%
3 – Moderate	87.1%	58.1%	61.3%	67.7%	54.8%	51.7%
4 – Severe	6.5%	6.5%	9.7%	3.2%	6.5%	3.4%

Table 11
Degree of Plaque Elevation Through Time

IDP-118	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Plaque Elevation						
Number of Subjects	59	59	59	59	59	55
0 – None	0.0%	10.2%	28.8%	33.9%	40.7%	32.7%
1 – Minimum	0.0%	37.3%	32.2%	28.8%	32.2%	21.8%
2 – Mild	15.3%	35.6%	23.7%	23.7%	16.9%	30.9%
3 – Moderate	79.7%	15.3%	13.6%	13.6%	10.2%	12.7%
4 – Severe	5.1%	1.7%	1.7%	0.0%	0.0%	1.8%
HP 0.01%						
Plaque Elevation						
Number of Subjects	63	63	63	63	63	62
0 – None	0.0%	9.5%	17.5%	20.6%	25.4%	22.6%
1 – Minimum	0.0%	14.3%	17.5%	33.3%	33.3%	30.6%
2 – Mild	17.5%	27.0%	36.5%	27.0%	22.2%	21.0%
3 – Moderate	73.0%	44.4%	27.0%	17.5%	17.5%	22.6%
4 – Severe	9.5%	4.8%	1.6%	1.6%	1.6%	3.2%

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Table 11 (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Taz 0.045%						
Plaque Elevation						
Number of Subjects	59	59	59	59	59	47
0 – None	0.0%	3.4%	3.4%	5.1%	5.1%	10.6%
1 – Minimum	0.0%	10.2%	28.8%	44.1%	39.0%	23.4%
2 – Mild	10.2%	40.7%	35.6%	23.7%	30.5%	31.9%
3 – Moderate	84.7%	42.4%	27.1%	23.7%	20.3%	31.9%
4 – Severe	5.1%	3.4%	5.1%	3.4%	5.1%	2.1%
Vehicle						
Plaque Elevation						
Number of Subjects	31	31	31	31	31	29
0 – Clear	0.0%	0.0%	3.2%	3.2%	6.5%	0.0%
1 – None	0.0%	6.5%	9.7%	3.2%	12.9%	17.2%
2 – Minimum	12.9%	29.0%	22.6%	29.0%	19.4%	37.9%
3 – Moderate	71.0%	61.3%	61.3%	61.3%	51.6%	34.5%
4 – Severe	16.1%	3.2%	3.2%	3.2%	9.7%	10.3%

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Table 12
Degree of Scaling Through Time

IDP-118	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Scaling						
Number of Subjects	59	59	59	59	59	55
0 – None	0.0%	6.8%	20.3%	20.3%	37.3%	29.1%
1 – Minimum	0.0%	37.3%	39.0%	50.8%	35.6%	38.2%
2 – Mild	16.9%	33.9%	33.9%	25.4%	18.6%	21.8%
3 – Moderate	76.3%	20.3%	6.8%	3.4%	8.5%	10.9%
4 – Severe	6.8%	1.7%	0.0%	0.0%	0.0%	0.0%
HP 0.01%						
Scaling						
Number of Subjects	63	63	63	63	63	62
0 – None	0.0%	4.8%	17.5%	20.6%	30.2%	21.0%
1 – Minimum	0.0%	22.2%	27.0%	33.3%	33.3%	30.6%
2 – Mild	15.9%	36.5%	36.5%	28.6%	22.2%	24.2%
3 – Moderate	73.0%	33.3%	17.5%	15.9%	12.7%	21.0%
4 – Severe	11.1%	3.2%	1.6%)	1.6%	1.6%)	3.2%

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Table 12 (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Taz 0.045%						
Scaling						
Number of Subjects	59	59	59	59	59	47
0 – None	0.0%	1.7%	0.0%	3.4%	1.7%	8.5%
1 – Minimum	0.0%	13.6%	23.7%	37.3%	37.3%	27.7%
2 – Mild	27.1%	37.3%	40.7%	22.0%	22.0%	25.5%
3 – Moderate	62.7%	39.0%	30.5%	33.9%	35.6%	36.2%
4 – Severe	10.2%)	8.5%	5.1%	3.4%	3.4%	2.1%
Vehicle						
Scaling						
Number of Subjects	31	31	31	31	31	29
0 – Clear	0.0%	0.0%	3.2%	0.0%	12.9%	3.4%
1 – None	0.0%	6.5%	19.4%	19.4%	16.1%	17.2%
2 – Minimum	16.1%	38.7%	25.8%	22.6%	25.8%	37.9%
3 – Moderate	67.7%	48.4%	41.9%	48.4%	38.7%	37.9%
4 – Severe	16.1%)	6.5%	9.7%	9.7%	6.5%	3.4%

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Table 13
Frequency of Local Skin Reactions Through Time

Itching	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
IDP-118						
Number of Subjects	59	59	57	57	55	55
0 – None	35.6%	52.5%	50.9%	57.9%	63.6%	67.3%
1 – Mild	23.7%	33.9%	40.4%	35.1%	20.0%	25.5%
2 – Moderate	39.0%	11.9%)	8.8%	5.3%	12.7%	7.3%
3 – Severe	1.7%	1.7%	0.0%	1.8%)	3.6%	0.0%
HP 0.01%						
Number of Subjects	62	62	62	61	62	62
0 – None	32.3%	46.8%	58.1%	59.0%	72.6%	38.7%
1 – Mild	21.0%	30.6%	32.3%	31.1%	16.1%	30.6%
2 – Moderate	32.3%	19.4%	9.7%	9.8%	11.3%	21.0%
3 – Severe	14.5%	3.2%	0.0%	0.0%	0.0%	9.7%
Taz 0.045%						
Number of Subjects	58	57	48	49	47	47
0 – None	29.3%	35.1%	35.4%	32.7%	36.2%	46.8%
1 – Mild	22.4%	26.3%	31.3%	36.7%	34.0%	38.3%
2 – Moderate	41.4%	26.3%	27.1%	24.5%	23.4%	12.8%
3 – Severe	6.9%	12.3%	6.3%	6.1%	6.4%	2.1%
Vehicle						
Number of Subjects	31	31	31	31	30	29
0 – None	22.6%	35.5%	45.2%	38.7%	33.3%	48.3%
1 – Mild	29.0%	35.5%	25.8%	25.8%	33.3%	27.6%
2 – Moderate	38.7%	19.4%	16.1%	25.8%	23.3%	20.7%
3 – Severe	9.7%	9.7%	12.9%	9.7%	10.0%	3.4%

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Table 13 (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Burning/Stinging						
IDP-118						
Number of Subjects	59	59	57	57	55	55
0 – None	71.2%	79.7%	73.7%	77.2%	70.9%	89.1%
1 – Mild	10.2%	13.6%	15.8%	12.3%	21.8%	10.9%
2 – Moderate	18.6%	6.8%	10.5%	8.8%	7.3%	0.0%
3 – Severe	0.0%	0.0%	0.0%	1.8%	0.0%	0.0%
HP 0.01%						
Number of Subjects	62	62	62	61	62	62
0 – None	62.9%	77.4%	79.0%	88.5%	91.9%	83.9%
1 – Mild	11.3%	14.5%	16.1%	9.8%	6.5%	9.7%
2 – Moderate	19.4%	6.5%	4.8%	1.6%	1.6%	4.8%
3 – Severe	6.5%	1.6%	0.0%	0.0%	0.0%	1.6%
Taz 0.045%						
Number of Subjects	58	57	48	49	47	47
0 – None	72.4%	63.2%	64.6%	57.1%	68.1%	85.1%
1 – Mild	10.3%	17.5%	18.8%	30.6%	19.1%	10.6%
2 – Moderate	17.2%	12.3%	14.6%	8.2%	12.8%	4.3%
3 – Severe	0.0%	7.0%	2.1%	4.1%	0.0%	0.0%
Vehicle						
Number of Subjects	31	31	31	31	30	29
0 – None	54.8%	71.0%	74.2%	71.0%	76.7%	72.4%
1 – Mild	19.4%	19.4%	16.1%	22.6%	3.3%	6.9%
2 – Moderate	22.6%	6.5%	3.2%	3.2%	13.3%	17.2%
3 – Severe	3.2%	3.2%	6.5%	3.2%	6.7%	3.4%

[0081] IDP-118 was consistently more effective than HP 0.01%, Taz 0.045%, or vehicle in achieving treatment success, defined as at least a two-grade improvement from Baseline in the IGA score at baseline and a score of Clear or Almost Clear at the evaluation time. IDP-118 demonstrated statistically significant superiority over vehicle as early as two weeks after starting treatment. At Week 8 end of treatment, 52.5% of subjects in the IDP-118 group had treatment success compared with 33.3% in the HP group, 18.6% in the Taz group, and 9.7% in the Vehicle group (see Table 5). Pairwise tests comparing IDP-118 with vehicle and HP 0.01% or Taz 0.045% showed statistically significant treatment group differences at both Week 8 (end of treatment) and Week 12 (4-week post-treatment follow-up). Of the subjects in the IDP-118 group who achieved treatment success at Week 8, more than half maintained status (treatment success) at Week 12 some four weeks after the completion of daily application of the test material, demonstrating the absence of a corticosteroid rebound effect.

[0082] Mean absolute and percent changes in the IGA score from Baseline at each visit were consistent with the results of the dichotomized IGA. At Week 8, the mean change from Baseline IGA score was -1.42 in the IDP-118 group compared with -1.24 in the HP group, -0.64 in the Taz group, and -0.42 in the Vehicle group.

[0083] There were no serious adverse reactions reported in any of the patients treated with IDP-118 during the eight-week period of daily application of the composition or the four-week medication-free follow-up period.

[0084] In another aspect, the present invention provides a method for treating psoriasis. The method comprises topically applying to an affected area of the body of a subject suffering from psoriasis 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 psoriasis. 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.

[0085] In yet another aspect, the present invention provides a method of treating psoriasis topically with pharmaceutical composition comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester; wherein each of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester is present in the composition at a positive

concentration of less than 0.05% based on the weight of the composition; wherein the clinical efficacy of the combination is greater than that of either the halobetasol component or the tazarotene component at the same concentration when used alone.

[0086] In yet another aspect, the present invention provides a method of treating psoriasis topically with pharmaceutical composition comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester; wherein each of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition; wherein the clinical success rate of the combination is synergistic compared to the clinical success rate of the halobetasol component at the same concentration used alone plus the clinical success rate of the tazarotene component used alone at the same concentration.

[0087] In yet another aspect, the present invention provides topical pharmaceutical compositions comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester thereof, and methods using the same, for treating psoriasis; wherein the pharmaceutical composition is a cream, lotion, ointment, gel, shampoo, suspension, paste, plaster, foam, spray

or solution. Prophetic examples of formulations of some of these types are illustrated in Table 14.

[0088] In yet another aspect, the present invention provides a method of treating psoriasis topically with pharmaceutical composition comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester; wherein the composition is applied at least once daily for 4 weeks, such as for 6 weeks or 8 weeks.

[0089] In yet another aspect, the present invention provides a method of treating psoriasis topically with pharmaceutical composition comprising a combination of: (a) halobetasol or a pharmaceutically acceptable salt, or ester thereof; and (b) a tazarotene or a pharmaceutically acceptable tazarotenic acid salt, or ester; wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks or for 8 weeks without any serious adverse events (side effects).

[0090] In yet another aspect, a composition of the present invention that can be used in any of the methods disclosed herein can be in the form of a solution, a spray, a milk, a foam, or an ointment. Non-limiting examples of these compositions are shown in Table 14.

Table 14

Examples of Various Dosage Forms of Compositions of the Present Invention

Ingredient	Concentration (% wt)				
	Solution	Spray	Milk	Foam	Ointment
Corticosteroid	0.001-0.049	0.001-0.049	0.001-0.049	0.001-0.049	0.001-0.049
Tazarotene or tazarotenic acid	0.01-0.049	0.01-0.049	0.01-0.049	0.01-0.049	0.01-0.049
Humectant	0 - 15.0	0 - 15.0	0 - 15.0	0 - 15.0	---
Antimicrobial preservative	0.01- 0.4	0.01- 0.4	0.01- 0.4	0.01- 0.4	---
Chelating agent	0.02 - 0.1	0.02 - 0.1	0.02 - 0.1	0.02 - 0.1	---
Emollients /Lipophilic Solvents	qsad 100	0.5 - 50.0	0.5 - 50.0	0.5 - 50.0	0.5 - 50.0
Volatile solvent	---	qsad 100	---	---	---
Non-ionic polyethoxylated compounds	---	---	---	---	---
Non-ionic sorbitan compounds	---	---	0.5 - 5.0	---	0.5 - 5.0
Polyoxyethylene fatty ethers	---	---	---	0.5 - 10.0	---
Fatty alcohols	---	---	---	1 - 8.0	1.0 - 10.0
Petrolatum	---	---	---	---	qsad 100
Pharmaceutical aids (pH adjustment)	---	---	0.1 - 5.0	0.1 - 5.0	---
Purified water	---	---	qsad 100	qsad 100	---

[0091] In still another aspect, a composition of the present invention may be used in conjunction with another method of treatment of psoriasis, such as phototherapy (e.g., with ultraviolet light).

[0092] In yet another aspect, a composition of the present invention may be used in conjunction with another medicament for treating psoriasis. Such other medicament may be an anti-TNF-α agent (e.g., infliximab, etanercept, adalimumab, or golimumab), an agent targeting the Th17/IL-23 axis (e.g., ustekinumab or briakinumab), a protein kinase C inhibitor (e.g., AEB071), a mitogen-activated protein kinase inhibitor (e.g., BMS-582949), a FMS-like tyrosine kinase inhibitor (e.g., lestaurtinib), a Janus kinase inhibitor tofacitinib, ASP-015K, or INCB018424), a phosphodiesterase 4 inhibitor (e.g., apremilast, AN2728, or MK0873), a nerve growth factor inhibitor (e.g., CF101), an anti-folate agent (e.g., methotrexate, aminopterin, or BCX-4208), a calcineurin inhibitor (e.g., cyclosporine), an anti-angiogenic agent (e.g., anti-VEGF antibody or soluble VEGFR), or a vitamin D analog or derivative. Such other medicament may be administered to a patient at substantially the same time or at a different time. Such other medication may be administered topically, orally, or by injection or infusion.

[0093] 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 the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

WHAT IS CLAIMED IS:

1. A topical pharmaceutical composition for treating psoriasis the composition comprising:

(a) a corticosteroid or a pharmaceutically acceptable salt or ester thereof, at a positive concentration of less than 0.05 percent by weight of the composition;

(b) a retinoid or a pharmaceutically acceptable salt or ester thereof at a positive concentration of less than 0.09 percent by weight of the composition; and

(c) a dermatologically acceptable carrier; wherein the corticosteroid is selected from the group consisting of halobetasol, clobetasol, betamethasone, diflorasone, and fluocinonide.

2. The topical pharmaceutical composition of claim 1, wherein the corticosteroid or a pharmaceutically acceptable salt or ester thereof is selected from the group consisting of halobetasol propionate, clobetasol propionate, betamethasone dipropionate, diflorasone diacetate, and fluocinonide.

3. The topical pharmaceutical composition of claim 1, wherein the retinoid is selected from the group consisting of tazarotene, bexarotene, and adapalene.

4. The topical pharmaceutical composition of claim 1, wherein the corticosteroid is halobetasol propionate, and the retinoid is tazarotene.

5. The topical pharmaceutical composition of claim 1, wherein (a) the corticosteroid is halobetasol or a pharmaceutically acceptable salt or ester thereof, and (b) the retinoid is tazarotene or a pharmaceutically acceptable tazarotenic acid salt, wherein (a) halobetasol or a pharmaceutically acceptable salt or ester thereof is present in the composition at a concentration in the range from about 0.005 to about 0.03 percent by weight of the composition, and (b) tazarotene or a

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pharmaceutically acceptable tazarotenic acid salt is present in the composition at a concentration in the range from about 0.005 to about 0.049 percent by weight of the composition.

6. The topical pharmaceutical composition of claim 1, comprising:

(a) halobetasol propionate at a concentration of 0.01 percent by weight of the composition; and

(b) tazarotene at a concentration of 0.045 percent by weight of the composition.

7. The topical pharmaceutical composition of claim 1, wherein the composition is an oil-in-water emulsion.

8. The topical pharmaceutical composition of claim 7, wherein the corticosteroid and the retinoid are dissolved in a liquid oil component of the emulsion.

9. The topical pharmaceutical composition of claim 7, wherein the liquid oil component comprises a DCAE, MCAE, or combinations thereof.

10. The topical pharmaceutical composition of claim 8, wherein the liquid oil component is selected from the group consisting of DCAE, MCAE, combinations thereof, and mixtures thereof.

11. The topical pharmaceutical composition of claim 7, wherein an oil phase of the oil-in-water emulsion comprises a liquid oil component, which comprises diethyl sebacate and light mineral oil.

12. The topical pharmaceutical composition of claim 11, wherein the corticosteroid and the retinoid are dissolved in the liquid oil component of the emulsion.

13. The topical pharmaceutical composition of claim 7, wherein the emulsion is a lotion.

14. The topical pharmaceutical composition of claim 7, wherein the emulsion is a cream.

15. A method of treating psoriasis, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from psoriasis, wherein the composition comprises:

(a) a corticosteroid or a pharmaceutically acceptable salt or ester thereof, at a positive concentration of less than 0.05 percent by weight of the composition;

(b) a retinoid or a pharmaceutically acceptable salt or ester thereof at a positive concentration of less than 0.09 percent by weight of the composition; and

(c) a dermatologically acceptable carrier; wherein the corticosteroid is selected from the group consisting of halobetasol, clobetasol, betamethasone, diflorasone, and fluocinonide; and wherein said applying is carried out one or more times per day for a period of time sufficient to treat such psoriasis.

16. The method of claim 15;,wherein said applying is carried out once per day for eight weeks.

17. The method of claim 15, wherein the corticosteroid or a pharmaceutically acceptable salt or ester thereof is selected from the group consisting of halobetasol propionate, clobetasol propionate, betamethasone dipropionate, diflorasone diacetate, and fluocinonide.

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18. The method of claim 15, wherein the retinoid is selected from the group consisting of tazarotene, bexarotene, and adapalene.

19. The method of claim 15, wherein the corticosteroid is halobetasol propionate, and the retinoid is tazarotene.

20. The method of claim 15, wherein (a) the corticosteroid is halobetasol or a pharmaceutically acceptable salt or ester thereof; and (b) the retinoid is tazarotene or a pharmaceutically acceptable tazarotenic acid salt; wherein (a) halobetasol or a pharmaceutically acceptable salt or ester thereof is present in the composition at a concentration in the range from about 0.005 to about 0.03 percent by weight of the composition; and (b) tazarotene or a pharmaceutically acceptable tazarotenic acid salt is present in the composition at a concentration in the range from about 0.005 to about 0.049 percent by weight of the composition.

21. The method of claim 15, comprising: (a) halobetasol propionate at a concentration of 0.01 percent by weight of the composition, and (b) tazarotene at a concentration of 0.045 percent by weight of the composition.

22. The method of claim 15, wherein the composition is an oil-in-water emulsion.

23. The method of claim 22, wherein the corticosteroid and the retinoid are dissolved in a liquid oil component of the emulsion.

24. The method of claim 22, wherein the liquid oil component comprises a DCAE, MCAE, or combinations thereof.

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25. The method of claim 23, wherein the liquid oil component comprises a DCAE, MCAE, or combinations thereof.

26. The method of claim 22, wherein an oil phase of the oil-in-water emulsion comprises a liquid oil component, which comprises diethyl sebacate and light mineral oil.

27. The method of claim 26, wherein the corticosteroid and the retinoid are dissolved in the liquid oil component of the emulsion.

28. The method of claim 22, wherein the emulsion is a lotion.

29. The method of claim 22, wherein the emulsion is a cream.

30. The method of claim 21, wherein said applying is carried out once per day for eight weeks.

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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

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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	Date of mailing of the international search report
3 August 2016	11/08/2016

Name and mailing address of the ISA/	Authorized officer
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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

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/035991

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

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[19] 中华人民共和国国家知识产权局

[12] 发明专利申请公开说明书

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A61K 31/4436 A61K 9/06
A61K 9/70 A61K 9/00
A61P 17/10
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权利要求书 1 页 说明书 6 页

[54] 发明名称 治疗痤疮的复方外用药物

[57] 摘要

本发明涉及一种治疗痤疮的复方外用药物。其特征在于：复方外用药物的基质载体中含有下列两种有效活性成分(重量百分比)：他扎罗汀 0.01～2%，抗菌药 0.25～5%；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，形成乳膏或凝胶或搽剂或涂膜剂。本发明的优点在于：本发明是以复方制剂形式包含维 A 酸类及抗菌类两类治疗痤疮的主成分，以同时发挥 3 种(及以上)的疗效作用(溶解角栓、调节角化、抗微生物、抗炎症、减轻皮脂分泌的继发因素等)，在药理学上发挥了互补及协同作用。

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1、一种治疗痤疮的复方外用药物，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 0.01~2%，抗菌药 0.25~5%。

2、根据权利要求 1 所述的治疗痤疮的复方外用药物，其特征在于：所述的基质载体中含有的有效活性成分中的抗菌药及其含量为盐酸克林霉素 0.5~2%，或磷酸克林霉素 0.5~2%，或红霉素 0.5~5%，或氯霉素 0.25~2%，或四环素 0.25~2.5%，或甲硝唑 0.5~5%，或替硝唑 0.5~5%，或塞克硝唑 0.5~5%，，或氧氟沙星 0.2~2%，或环丙沙星 0.2~2%。

3、根据权利要求 1 所述的治疗痤疮的复方外用药物，其特征在于：所述的复方外用药物含有的两种有效活性成分与基质载体混合后，形成乳膏或凝胶或搽剂或涂膜剂。

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治疗痤疮的复方外用药物

技术领域：

本发明涉及一种治疗痤疮的外用药物，尤其是一种治疗痤疮的复方外用药物。

背景技术：

痤疮是皮脂腺慢性疾病，可分为炎性及非炎性痤疮两类，是皮肤科第二大常见病，发病率约占皮肤病 7~10%，患病年龄覆盖 11~30 岁间，男女皆可罹患。

现已知下述四种发病因素及环节在痤疮发生、发展及转归中起关键作用：1、毛囊及皮脂腺单位中的微生物作用，首先是厌氧的丙酸痤疮杆菌，次为需氧的表皮及金黄色葡萄球菌等优势化脓菌，有认为酵母菌属亦参与发病；2、雄激素及皮脂腺功能亢进，前者包括雄激素一受体亲和力增高和/或 5a-还原酶活性增强，使高活性的 2H-睾酮增多；后者主要指雄激素依赖性的皮脂腺增生和皮脂分泌增多；3、毛囊皮脂腺导管角化异常，最终导致毛囊口粉刺形成及角质栓塞，并诱发及加剧炎症；4、炎症的启动及毛囊-皮脂腺的炎症的毁坏。

药物是治疗座疮的主要手段，抗痤疮的药物是国内外皮肤科药物研究的热点，其作用原理主要围绕和针对上述发病环节。药物抗痤疮分系统及局部两种途径，局部治疗主要针对轻度痤疮及参与中度痤疮的治疗，重度痤疮在综合疗法的前提下也需要局部治疗加以配合。对于炎性痤疮主要治

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则是抗菌、消淡；对于非炎性痤疮主要治则是溶解粉刺。

现有治疗痤疮的药物多为单方，作用比较单一。例如主要针对炎性痤疮的药物多为抗生素，包括红霉素、克林霉素（包括磷酸盐及盐酸盐）、氯霉素，主要起抗菌作用，兼有抗炎作用；而主要针对非炎性痤疮的药物有维 A 酸类，过氧化苯甲酰、水杨酸、乳酸等，其中过氧化苯甲酰同时有很强的抗菌作用。

单方治疗存在的主要问题是作用单一，最多只能针对 1—2 个发病环节（如抗菌加抗炎，或抗菌加抗角栓）。此外，上述粉刺溶角药物多有局部刺激和/或过敏作用，过氧化苯甲酰有强氧化作用，如组成复方制剂，质量不易稳定，使配伍药物浓度，疗效波动，保存条件、保质期和使用方便性等方面都受到较大影响。

发明内容：

本发明的目的在于：针对治疗痤疮的单方制剂使用中存在的问题，提供一种新的主治痤疮的复方外用药物。

本发明的目的是这样实现的：一种治疗痤疮的复方外用药物，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 0.01~2%，抗菌药 0.25~5%。

维 A 酸类药物局部应用是有效的抗痤疮药物，局部适用于轻、中度痤疮，其作用原理为溶解粉刺，使毛囊-皮脂腺炎症得以引流，不利于厌氧菌生长，使药物易于透入毛囊皮脂腺内以增强抑、杀菌作用。同时还可调节上皮细胞分化，减少角栓形成以及有抗白细胞趋化的抗炎作用。

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他扎罗汀与第一代维 A 酸类药物相比的优势在于，受体选择性强，作用靶位明确，稳定性较好，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，几乎无全身不良反应。

本复方中选用的抗菌药物的共同特点是：这些药物对痤疮发病相关的主要病原菌如厌氧丙酸痤疮杆菌及需氧皮肤化脓菌（金黄色葡萄球菌，表皮葡萄球菌，链球菌等）都有抑制作用，从而减轻和消除发病的感染环节。

此外，本研究组已发现所选用的抗菌药物在抗菌的同时，还具有抑制白细胞趋化活性，这对抑制炎症介质的释放，减轻组织破坏，减少刺激皮脂分泌诱因，阻断痤疮炎症环节的启动及发展，缓解痤疮临床炎症症状起到重要作用。

由此可见，本发明的优点在于：本发明是以复方制剂形式包含维 A 酸类及抗菌类两类治疗痤疮的主成分，以同时发挥 3 种（及以上）的疗效作用（溶解角栓、调节角化、抗微生物、抗炎症、减轻皮脂分泌的继发因素等）在药理学上发挥了互补及协同作用，使治疗作用更全面、深入，疗效更满意。

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）和盐酸（或磷酸）克林霉素 1%，基质载体采用十六醇、凡士林、液体石蜡、单硬脂酸甘油酯、甘油、增溶剂、乳化剂、羟苯乙酯和蒸馏水。

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实施例 2：

本实施例的有效活性成分采用他扎罗汀 0.05%和红霉素 2%，基质载体采用十六醇、凡士林、液体石蜡、单硬脂酸甘油酯、甘油、增溶剂、乳化剂、羟苯乙酯和蒸馏水。

实施例 3：

先将实施例 1 或实施例 2 中的两种有效活性成分及 0.1%的羟苯乙酯溶于增溶剂中；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酯的增溶剂，搅拌均匀形成乳膏。

实施例 4：

本实施例的有效活性成分采用他扎罗汀 0.1 和氯霉素 0.5%，基质载体采用卡波姆、乙醇、丙二醇、EDTA-2Na、羟苯乙酯、中和剂和蒸馏水。

实施例 5：

本实施例的有效活性成分采用他扎罗汀 0.025%和四环素 2%，基质载体采用卡波姆、乙醇、丙二醇、EDTA-2Na、羟苯乙酯、中和剂和蒸馏水。

实施例 6：

先将实施例 4 或实施例 5 中的两种有效活性成分溶于总量 5~20%的乙醇中，总量 0.1%的羟苯乙酯溶于总量 0.01~2%的丙二醇中；用适量的

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蒸馏水加总量 0.05~2%的 EDTA-2Na 溶解，加入总量 1~10%的卡波姆溶胀成胶；将上述的溶液加入溶胶中搅拌均匀，用适量的中和剂将 PH 值调至 5~7，搅拌均匀形成凝胶。

实施例 7：

本实施例的有效活性成分采用他扎罗汀 0.05%和甲硝唑 2%，基质载体采用甘油、助溶剂、氮酮、抗氧剂和乙醇。

实施例 8：

本实施例的有效活性成分采用他扎罗汀 0.025%和替硝唑 1%，基质载体采用甘油、助溶剂、氮酮、抗氧剂和乙醇。

实施例 9：

本实施例的有效活性成分采用他扎罗汀 0.05%和塞克硝唑 2%，基质载体采用甘油、助溶剂、氮酮、抗氧剂和乙醇。

实施例 10：

先将实施例 7 或实施例 8 或实施例 9 中的两种有效活性成分溶于适量的助溶剂中，并将总量 10~15%的甘油、适量的氮酮、抗氧剂溶于适量的乙醇中，待所有成分溶解后，再加入适量的乙醇直至药物制剂的总重量，搅拌均匀形成搽剂。

实施例 11：

本实施例的有效活性成分采用他扎罗汀 0.05%和氧氟沙星 0.5%，基质载体采用增溶剂、甘油、成膜剂和蒸馏水。

实施例 12：

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本实施例的有效活性成分采用他扎罗汀 0.025%和环丙沙星 0.5%，基总量质载体采用增溶剂、甘油、成膜剂和蒸馏水。

实施例 13：

先将实施例 10 中的两种有效活性成分溶于增溶剂中；用适量的蒸馏水将成膜剂溶胀成胶状后加入总量 5~30%的甘油混匀，将溶有两种有效活性成分增溶剂加入溶胀的胶状物中，再加入适量的蒸馏水直至药物制剂的总重量，搅拌均匀形成涂膜剂。

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Complex external medicine for treating acne

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Abstract of CN1528328 (A)

The present invention relates to a compound medicine for external application for curing acne. Its composition contains the following two active components: (wt%) 0.01-2% of tazarotene and 0.25-5% of antimicrobial. Said compound medicine can be made into emulsifiable paste or gel or liniment or film preparation. Said compound medicine has the following therapeutic functions: dissolving keratotic plug, regulating keratosis, resisting microbe, relieving inflammation and reducing secondary factor of sebaceous secretion, so that it can obtain obvious therapeutic effect.

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DESCRIPTION CN1528328

Compound topical medicine for treating acne

Technical field:

The present invention relates to a topical medicine for treating acne, and more particularly to a compound for external use for treating acne.

Background technique:

Acne is a chronic disease of sebaceous glands, which can be divided into inflammatory and non-inflammatory acne. It is the second most common dermatological disease. The incidence rate is about 7-10% of skin diseases. The age of the disease covers 11 to 30 years old. Can suffer.

It is known that the following four pathogenic factors and links play a key role in the occurrence, development and outcome of acne: 1. Microbial action in hair follicles and sebaceous gland units, firstly anaerobic acne propionate, followed by aerobic Epidermis and Staphylococcus aureus and other dominant pyogenic bacteria, it is believed that yeast is also involved in the disease; 2, androgen and sebaceous gland hyperfunction, the former includes androgen-receptor affinity and / or 5a-reductase activity is enhanced, making high Active 2H-testosterone increased; the latter mainly refers to androgen-dependent sebaceous gland hyperplasia and increased sebum secretion; 3, hair follicle sebaceous gland ductal keratinization abnormalities, eventually leading to hair follicle acne formation and horny embolism, and induce and exacerbate inflammation; The initiation of inflammation and the inflammation of the hair follicle-spleen glands are destroyed.

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Drugs are the main means of treating acne. Anti-acne drugs are the hotspots of dermatology research at home and abroad. The principle of action mainly focuses on and targets the above-mentioned pathogenesis. The drug is resistant to hemorrhoids and localized. The local treatment is mainly for mild acne and the treatment of moderate acne. Severe acne also requires local treatment in combination with the comprehensive treatment. The main treatment for inflammatory acne is antibacterial and lightening; the main treatment for non-inflammatory acne is to dissolve acne.

The existing drugs for the treatment of acne are mostly unilateral, and the effect is relatively simple. For example, the main drugs for inflammatory acne are antibiotics, including erythromycin, clindamycin (including phosphate and hydrochloride), chloramphenicol, which mainly play an antibacterial role, and have anti-inflammatory effects; The drugs for inflammatory acne include vitamin A acid, benzoyl peroxide, salicylic acid, lactic acid, etc., wherein benzoyl peroxide has a strong antibacterial effect.

The main problem with unilateral treatment is that it has a single effect, and can only target at most 1-2 diseased joints (such as antibacterial plus anti-inflammatory, or antibacterial plus anti-angle plug). In addition, the above-mentioned acne-dissolving drugs have local irritation and/or allergic effects, and benzoyl peroxide has strong oxidation effect, such as composing compound preparation, the quality is not easy to be stable, the compatibility drug concentration, the curative effect fluctuation, the storage condition, the shelf life and the use Convenience and other aspects have been greatly affected.

Summary of the invention:

It is an object of the present invention to provide a novel topical topical medicine for treating acne in response to problems in the use of a single preparation for treating acne.

The object of the present invention is achieved by a compound for external use for treating acne, characterized in that the matrix carrier of the compound for external use contains the following effective active ingredients (% by weight): tazarotene 0.01 to 2%, antibacterial agent 0.25 to 5%.

Topical application of vitamin A acid is an effective anti-acne medicine, which is suitable for mild to moderate acne. Its principle of action is to dissolve acne, so that the hair follicle-sebace gland inflammation can be drained, which is not conducive to the growth of anaerobic bacteria, making the drug easy to penetrate. The hair follicle sebaceous glands enhance the inhibition and bactericidal action. It also regulates epithelial cell differentiation,

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reduces horn plug formation, and has anti-inflammatory effects against leukocyte chemotaxis.

The advantage of tazarotene compared with the first-generation retinoic acid is that the receptor has strong selectivity, clear target, good stability, local application mainly remains in the skin, rapid metabolism, almost no transdermal penetration. In the system, local skin irritation is relatively light and there is almost no systemic adverse reaction.

The common features of the antibacterial drugs selected in this compound are: These drugs have major pathogens related to the development of acne, such as anaerobic acne acne and aerobic skin pyogenic bacteria (Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus, etc.) Inhibition, thereby reducing and eliminating the onset of infection.

In addition, the research team has found that the selected antibacterial drugs also inhibit leukocyte chemotactic activity while inhibiting the release of inflammatory mediators, reducing tissue damage, reducing the incentives for sebum secretion, and blocking the initiation of acne inflammation. And development, to relieve the clinical symptoms of acne, play an important role.

It can be seen that the present invention has the advantages that the present invention comprises a main component of acne and antibacterial treatments in the form of a compound preparation, and simultaneously exerts three (and above) therapeutic effects (dissolved angle plug, Regulating keratinization, anti-microbial, anti-inflammatory, and secondary factors that reduce sebum secretion, etc.) play a complementary and synergistic role in pharmacology, making the treatment more comprehensive, deeper, and more satisfactory.

Detailed ways:

Some of the embodiments of the present invention are exemplified below without limitation.

Example 1:

The effective active ingredient of the present embodiment is 0.1% (by weight, the same below) and 1% by weight of hydrochloric acid (or phosphoric acid) clindamycin, and the substrate carrier is cetyl alcohol, petrolatum, liquid paraffin, and monostearic acid. Glycerides, glycerin, solubilizers, emulsifiers, hydroxyethyl esters and distilled water.

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Example 2:

The effective active ingredient of the present embodiment comprises tazarotene 0.05% and erythromycin 2%, and the matrix carrier uses cetyl alcohol, petrolatum, liquid paraffin, glyceryl monostearate, glycerin, solubilizer, emulsifier, hydroxybenzene. Ethyl ester and distilled water.

Example 3:

Firstly, the two effective active ingredients in Example 1 or Example 2 and 0.1% hydroxyethyl ester are dissolved in a solubilizing agent; and the total amount is 8-12% of cetyl alcohol, and the total amount is 5-10%. Vaseline, a total of 8 to 12% of liquid paraffin, a total amount of 5 to 10% of glyceryl monostearate and an appropriate amount of emulsifier are mixed and heated to 80 to 85 ° C; a total amount of 0.5 to 5% of glycerol and appropriate amount The distilled water is mixed and heated to 80-85 ° C, and mixed with the above mixture of cetyl alcohol, petrolatum, liquid paraffin, glyceryl monostearate and emulsifier; the emulsified mixture is removed from the heat source, stirred and cooled to At 65 ° C, a solubilizer in which two effective active ingredients and hydroxyphenylethyl ester are dissolved is added and stirred to form a cream.

Example 4:

The effective active ingredient of this example was tazarotene 0.1 and chloramphenicol 0.5%, and the matrix carrier was carbomer, ethanol, propylene glycol, EDTA-2Na, hydroxyethyl ester, neutralizer and distilled water.

Example 5:

The effective active ingredient of this example was tazarotene 0.025% and tetracycline 2%, and the matrix carrier was carbomer, ethanol, propylene glycol, EDTA-2Na, hydroxyethyl ester, neutralizer and distilled water.

Example 6

Firstly, the two effective active ingredients in Example 4 or Example 5 are dissolved in a total amount of 5-20%

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ethanol, and a total amount of 0.1% of hydroxyethyl ester is dissolved in a total amount of 0.01 to 2% of propylene glycol; Appropriate amount of distilled water is added with a total amount of 0.05~2% of EDTA-2Na dissolved, and a total of 1~10% of carbomer is added to swell into a gel; the above solution is added to the sol and stirred uniformly, and the pH is adjusted with an appropriate amount of neutralizing agent. Adjust to 5-7, stir evenly to form a gel.

Example 7

The effective active ingredient of this example was tazarotene 0.05% and metronidazole 2%, and the matrix carrier was glycerin, a cosolvent, an azone, an antioxidant and ethanol.

Example 8

The effective active ingredient of this example was tazarotene 0.025% and tinidazole 1%, and the matrix carrier was glycerin, co-solvent, azone, antioxidant and ethanol.

Example 9

The effective active ingredient of this example was tazarotene 0.05% and secnidazole 2%, and the matrix carrier was glycerin, a cosolvent, an azone, an antioxidant and ethanol.

Example 10:

Firstly, the two effective active ingredients in Example 7 or Example 8 or Example 9 are dissolved in an appropriate amount of a cosolvent, and a total amount of 10-15% of glycerin, an appropriate amount of azone, and an antioxidant are dissolved in an appropriate amount. In the ethanol, after all the ingredients are dissolved, an appropriate amount of ethanol is added until the total weight of the pharmaceutical preparation is stirred to form an elixir.

Example 11

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The effective active ingredient of this example was tazarotene 0.05% and ofloxacin 0.5%, and the base carrier was a solubilizer, glycerin, a film former and distilled water.

Example 12

The effective active ingredient of this example employs 0.025% of tazarotene and 0.5% of ciprofloxacin. The base carrier is a solubilizer, glycerin, a film former and distilled water.

Example 13

First, the two effective active ingredients in the embodiment 10 are dissolved in a solubilizing agent; the film forming agent is swollen into a gel with an appropriate amount of distilled water, and then a total amount of 5 to 30% of glycerin is added and mixed, and two effective activities are dissolved. The component solubilizer is added to the swollen gel, and an appropriate amount of distilled water is added until the total weight of the pharmaceutical preparation is stirred to form a coating agent.

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CLAIMS CN1528328

1、
A compound external preparation for treating acne, characterized in that the base carrier of the compound external preparation contains the following effective active ingredients (weight percentage): tazarotene 0.01 to 2%, and antibacterial drug 0.25 to 5%.

2、
The compound for external use for treating acne according to claim 1, wherein: the antibacterial agent in the effective active ingredient contained in the matrix carrier and the content thereof are 0.5 to 2% of clindamycin hydrochloride, or gram of phosphate Linmycin 0.5~2%, or erythromycin 0.5～5%, or chloramphenicol 0.25～2%, or tetracycline 0.25～2.5%, or metronidazole 0.5～5%, or tinidazole 0.5～5% , or secnidazole 0.5 to 5%, or ofloxacin 0.2 to 2%, or ciprofloxacin 0.2 to 2%.

3、
The compound for external use for treating acne according to claim 1, wherein: the compound external preparation contains two effective active ingredients mixed with a matrix carrier to form a cream or gel or a tincture or a coating agent. .

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(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING CORTICOSTEROIDS FOR TOPICAL ADMINISTRATION

(57) Abstract: The potency of a topical corticosteroid in a pharmaceutical formulation is maintained even when the concentration of the corticosteroid is substantially reduced by providing the corticosteroid in a formulation containing a liquid oil component that includes a dicarboxylic acid ester and/or a monocarboxylic acid ester.

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PHARMACEUTICAL FORMULATIONS CONTAINING CORTICOSTEROIDS FOR TOPICAL ADMINISTRATION

Background of the Invention

Topical corticosteroids are used to treat many acute and chronic dermatologic and mucosal disorders, especially those in which pruritus or inflammation is present. Many such conditions, such as eczema, psoriasis, and chronic dermatitis, such as hand dermatitis, are chronic conditions that require long-term therapy.

Corticosteroids for topical application are grouped within a classification system into seven classes based on potency. Topical potency of a corticosteroid is determined by a standard test, referred to as a VasoConstrictor Assay (VCA). The VCA test is described in Dow et al, US Patent No. 7,300,669, incorporated herein by reference.

Table 1 shows the classification of topical corticosteroids based on potency as determined by the VCA test.

Potency Chart of Topical Corticosteroids
Class 1 - Superpotent
Clobetasol propionate 0.05%
Betamethasone dipropionate ointment 0.05%
Halobetasol propionate 0.05%
Fluocinonide 0.1%
Diflorasone diacetate ointment 0.05% (Psorcon©)
Class 2 - Potent
Betamethasone dipropionate cream 0.05%
Mometasone furoate ointment 0.1%
Diflorasone diacetate cream 0.05% (Psorcon©)
Diflorasone diacetate ointment 0.05% (Florone©)
Halcinonide 0.1%
Desoximetasone cream/ointment 0.25%
Desoximetasone gel 0.05%
Fluocinonide cream/gel/ointment 0.05% (Lidex©)
Amcinonide 0.1%
Budesonide 0.025%
Beclomethasone 0.025%

Class 3 - Upper Mid-strength
Fluticasone propionate ointment 0.005%
Fluocinonide cream 0.05% (Lidex-E®)
Betamethasone valerate 0.12%
Desoximetasone cream 0.05%
Class 4 - Mid-strength
Flurandrenolide ointment 0.05%
Mometasone furoate cream 0.1%
Triamcinolone acetonide 0.1%
Fluocinolone acetonide 0.03%
Hydrocortisone valerate 0.2%
Class 5 - Lower Mid-strength
Fluocinolone acetonide shampoo 0.01%
Flurandrenolide cream/lotion/tape 0.05%
Fluticasone propionate cream/lotion 0.05%
Prednicarbate cream 0.1%
Desonide lotion 0.05%
Hydrocortisone butyrate cream/lotion/ointment/solution 0.1% (Locoid®)
Hydrocortisone probutate cream 0.1% (Pandel®)
Fluocinolone acetonide cream 0.03%/0.01% (Synalar®)
Hydrocortisone valerate cream 0.2%
Class 6 - Mild
Alclometasone dipropionate 0.05%
Fluocinolone acetonide oil 0.01%
Desonide gel 0.05%
Fluocinonide cream/solution 0.01%
Desonide foam 0.05%
Class 7 - Least Potent
Hydrocortisone lotion 0.5%/1%
Hydrocortisone cream/spray/ointment 1%
Hydrocortisone cream lotion 1%/2.5%

Table 1

The most potent group of corticosteroids, determined on the basis of the VCA, is denoted Class 1 superpotent corticosteroids. In this specification, when a concentration is indicated with a particular corticosteroid, for example as an ester, an acetonide, a free alcohol, or a diester, the corticosteroid is stated as a particular form of the corticosteroid. When no concentration is indicated with a corticosteroid, or when a concentration refers to the corticosteroid in more than one form, such as an ester, an acetonide, a free alcohol, or a diester, the corticosteroid is stated without reference to the particular form. All known

preparations of clobetasol propionate and halobetasol propionate, all of which are at a concentration of 0.05% w/w, are classed as superpotent corticosteroids. Other corticosteroids classified as superpotent are certain preparations of betamethasone dipropionate at a concentration of 0.05%, diflorasone diacetate at a concentration of 0.05%, and fluocinonide at a concentration of 0.1%. The next most potent group of corticosteroids is denoted Class 2 potent corticosteroids. This group includes mometasone furoate at a concentration of 0.1%, halcinonide, diflorasone diacetate, desoximetasone, fluocinonide at a concentration of 0.05%, and cream formulations of betamethasone at a concentration of 0.05%.

The superpotent corticosteroids are utilized for skin conditions that are not satisfactorily responsive to lower potency corticosteroids. Such conditions include psoriasis and certain severe types of eczema. Unfortunately, because of the high potency of the Class I corticosteroids, which correlates with a high incidence and severity of systemic side effects, including hypothalamic-pituitary-adrenal (HPA) axis suppression, topical treatment with superpotent corticosteroids is generally limited in duration to 2 weeks. Such side effects may also occur with treatment with Class 2 potent corticosteroids. Additionally, the occurrence of local adverse reactions limits the duration of use of superpotent and potent corticosteroids with respect to treatment of chronic or recurrent skin diseases.

Chronic skin conditions, such as psoriasis, however often require long periods of treatment, greater than 2 weeks, to manage such conditions. Therefore, it would be desirable to have a superpotent corticosteroid formulation with a reduced incidence and/or severity of systemic side effects so that therapy can be continued for durations longer than 2 weeks.

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Dow, U.S. Patent Publication 2006/0239929 discloses a spray formulation containing 0.05% clobetasol that was shown to be efficacious and to have few serious side effects when administered for periods of 4 weeks. The disclosure of Dow, however, was limited to a spray formulation and the prosecution history of this application shows that prior art formulations of 0.05% clobetasol are associated with high frequencies of serious systemic side effects, including hypothalamic-pituitary-adrenal axis suppression when applied for a period of 2 weeks.

Because of the tendency of all superpotent corticosteroids to cause serious systemic effects, the FDA (Food and Drug Administration) requires that the prescribing information for currently marketed topical compositions of superpotent corticosteroids, such as clobetasol and halobetasol, except for a particular spray formulation of clobetasol, carry the warning that treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g of the composition per week. Regarding the clobetasol spray formulation, the prescribing information states that treatment should be limited to 4 weeks and that treatment beyond 2 weeks should be limited to localized lesions of moderate to severe plaque psoriasis that have not sufficiently improved after two weeks. Regarding potent corticosteroids, the FDA does not require the prescribing information to carry this warning, but does caution the physician to be aware of and to monitor for the occurrence of HPA axis suppression.

Busse, U.S. Patent No. 4,370,322, concerns the problem of systemic side effects due to topical application of high-potency corticosteroids. Busse discloses a topical pharmaceutical composition containing a high-potency corticosteroid and an oil phase that contains a low viscosity oily solvent, wherein the concentration of the liquid oil

phase is at least three times that which is required to completely solubilize the corticosteroid. Busse discloses that, when the solvent-containing oil phase is present in such high concentrations relative to the corticosteroid, the systemic absorption of the corticosteroid is reduced but the local, desirable effects of the corticosteroid are maintained. Busse further disclose that this discovery permits the application of the same amount of steroid to achieve the same local anti-inflammatory effect while reducing unwanted systemic effects.

Parab, U.S. Patent No. 5,326,566, in contrast to the disclosure of Busse which discloses that a high concentration oily phase will decrease systemic absorption of a corticosteroid when applied to the skin, discloses that, when a formulation contains a skin penetration enhancing amount of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate at a concentration that is sufficient to dissolve the corticosteroid in the formulation but which is less than 1.5 times that which is required to dissolve the corticosteroid, the penetration of the corticosteroid through skin and into the systemic circulation is increased rather than decreased. Thus, Parab discloses that formulations containing a corticosteroid and an oily phase containing dibutyl adipate, alone or in combination with isopropyl myristate, at a concentration between 1 and 1.5 times that required to dissolve the corticosteroid are useful for increasing the systemic absorption of a topically applied corticosteroid.

Description of the Invention

It has been unexpectedly discovered that the potency of a topical corticosteroid, including superpotent and potent topical corticosteroid as determined by VCA test described above, is maintained even when the concentration of the

corticosteroid is substantially reduced by providing the corticosteroid in a formulation containing a liquid oil component that includes a dicarboxylic acid ester and/or a monocarboxylic acid ester. Because the potency of the corticosteroid is maintained, even when the concentration of the corticosteroid is markedly reduced, the desired dermatological effects of the treatment are obtained. Due to the much reduced concentration of the corticosteroid in the formulation, reduced amounts of corticosteroid are available to enter the systemic circulation and, therefore, the tendency of such formulations to cause undesirable systemic side effects should likewise be reduced. Thus, the formulations and methods of this application are especially useful for the treatment of chronic or recalcitrant skin diseases, such as psoriasis, due to the concerns regarding safety when topical corticosteroids are used in multiple course treatments over time.

Accordingly, one embodiment of the invention is a pharmaceutical formulation for topical administration to the skin which contains a corticosteroid at a concentration below that which is presently utilized in topical formulations and which provides substantially an equivalent potency to formulations having the higher concentrations that are presently utilized. Thus, for superpotent corticosteroids other than fluocinonide, such as halobetasol propionate and clobetasol propionate, the formulation contains the corticosteroid at a concentration less than 0.05% w/w and for fluocinonide the formulation contains the corticosteroid at a concentration less than 0.05% w/w. Similarly, for potent corticosteroids other than mometasone, halcinonide, and beclomethasone, the formulation contains the corticosteroid at a concentration less than 0.05%, and in the case of mometasone or halcinonide, less than 0.1%, and in the case of beclomethasone, less than 0.025%.

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The liquid oil component of the present application includes all ingredients of the formulation that are practically insoluble or insoluble in water and which are liquid at room temperature of 22° C. Other than the dicarboxylic acid ester and monocarboxylic acid esters discussed herein, the liquid oil component may contain additional components such as hydrocarbons like mineral oil, light mineral oil, squalene, and squalane, fatty alcohols such as octylododecanol and isostearyl alcohol, fatty acids such as isostearic acid and oleic acid, and triglycerides such as peanut oil, and fractionated coconut oil.

In addition to the liquid oil component, the formulation may contain water insoluble or practically insoluble ingredients that are not liquid at room temperature. However, as discussed in further detail below, it is the liquid oil component of the formulation that is of importance in relation to the reduced concentration of the corticosteroid in the formulation.

The liquid oil component containing the dicarboxylic acid ester and/or the monocarboxylic acid ester in the formulation is in association with the corticosteroid in the formulation, such that the liquid oil component and the corticosteroid may interact in the formulation in order to dissolve or substantially dissolve the corticosteroid. It is hypothesized that it is this solubilization within the formulation that, upon application of the formulation to the skin of a patient, provides delivery of the corticosteroid preferentially into the skin rather than providing transdermal delivery through the skin and into the systemic circulation. As used herein, the term "substantially dissolve" means that the liquid oil component of a formulation of this invention can dissolve 25% or more of the corticosteroid in the formulation at a room temperature of 22°C.

The corticosteroid that is included in the formulation of the invention is preferably a superpotent corticosteroid according to the VasoConstrictor Assay (VCA), such as clobetasol, halobetasol, betamethasone dipropionate in augmented formulations, diflorasone diacetate in augmented formulations, and fluocinonide at 0.1%, or a potent corticosteroid, such as betamethasone dipropionate, mometasone furoate, diflorasone diacetate, halcinonide, fluocinonide, and desoximetasone.

Other steroids that are suitable for the formulation of the invention include corticosteroids other than superpotent or potent corticosteroids. Any corticosteroid that is suitable for topical application to the skin or mucous membrane of a human may be the corticosteroid of the formulation. The benefits of increased efficacy at lower concentration include reduced systemic exposure to the corticosteroid, increased local as well as systemic safety, and reduced cost of materials for making the therapeutic corticosteroid formulation. These benefits are applicable to corticosteroids of any potency, such as a corticosteroid of potency classes 3 to 7, upper mid-strength to least potent. For example desonide gel or foam is a class 6 mild corticosteroid and desonide lotion is a class 5 lower mid-strength corticosteroid. Desonide is widely used in children at a concentration of 0.05%. It is conceived that a formulation containing a concentration of desonide of less than 0.05% in which the potency is similar to that of formulations containing 0.05% desonide would be especially useful in order to reduce the total amount of steroid exposure experienced by children treated with desonide. Thus, included within the present invention are formulations containing concentrations of particular corticosteroids below those shown in Table 1. For example, the invention pertains to concentrations less than 0.005% for fluticasone propionate,

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concentrations less than 0.01% for fluocinolone acetonide, concentrations less than 0.025% for budesonide, beclomethasone, and triamcinolone acetonide, concentrations less than 0.05% for flurandernolide, desonide, and aclometasone dipropionate, concentrations less than 0.1% for amcinonide, betamethasone valerate, prednicarbate, hydrocortisone butyrate, and hydrocortisone probutate, and concentrations less than 0.2% for hydrocortisone valerate. The invention may also be practiced with any form of a corticosteroid, such as an ester, diester, free alcohol, or acetonide form of a corticosteroid.

The dicarboxylic acid ester (DCAE) that is suitable for the present invention has the formula $R_1OOC-(CH_2)n-COOR_2$, where 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 where n is straight or branched and 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 $CH_3CH_2OOC-(CH_2)_8-COOCH_2CH_3$. Diethyl sebacate is considered to be typical of the dicarboxylic acid esters disclosed as each of the parameters R_1, R_2, and n of diethyl sebacate are approximately in the center of the range of each of the specified parameters.

Examples of other suitable dicarboxylic acid esters where $R_1 = R_2$ 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 $R_1 \neq R_2$ 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.

Alternatively, or in combination with the DCAE, the formulation may contain a monocarboxylic acid ester (MCAE). The MCAE that is suitable for the present invention has the formula $CH_3-(CH_2)_n-COOR_1$, where R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and where n is straight or branched and 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.

The corticosteroid composition of the present invention may be any formulation that incorporates DCAE and/or MCAE such as ointments, solutions, gels, foams and emulsions including creams and lotions. Preferably, the formulation is an emulsion in which an internal oil component is dispersed within an external aqueous phase or an internal aqueous phase is dispersed within an external oil component. Examples of emulsions include water-in-oil, oil-in-water, water-in-oil-in-water emulsion, and oil-in-water-in-oil emulsions. The emulsion may be a macroemulsion, a microemulsion, or a nanoemulsion. Also contemplated are other formulations in which an oil phase and a water phase coexist within the formulation, such as a multivesicular emulsion, which is not a true emulsion, disclosed in Espinoza, U.S. Patent No. 6,709,663. Also contemplated is a liposomal dispersion in which, preferably, the DCAE is incorporated in the lipid component of the liposomes. Also contemplated are other formulations in which non-polar and polar liquid ingredients coexist with the formulation.

Preferably, the formulation of the invention contains a thickening agent to provide viscosity so that the formulation may be provided in the form of a lotion, gel, cream, or ointment. Preferably but not necessarily, the

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thickening agent is miscible or soluble in an aqueous fluid. Examples of suitable thickening agents include acacia, alginic acid, bentonite, carbomers, also known as carboxy vinyl polymers, such as sold under the tradename Carbopol® (Lubrizol, Wickliffe, Ohio), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, poloxamers, polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum. 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.

If desired or required in order to obtain the form of the formulation desired, a surfactant or emulsifier may be included. The emulsifier is preferably a non-ionic emulsifier such as a sorbitan ester, a polyoxyethylene derivative of a sorbitan ester or a glyceryl ester; a polymeric emulsifier such as a acrylates/C10-C30 alkyl acrylate crosspolymer such as those sold under the tradename PEMULEN® (The Lubrizol Corporation, Wickliffe, OH); or an anionic emulsifier such as an alkali soap such as sodium or potassium oleate, an amine soap such as triethanolamine stearate, a detergent such as sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Particular examples of suitable anionic and non-ionic 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.

The formulation may contain other pharmaceutically acceptable excipients. Preferably, the formulation contains a humectant such as glycerin, sorbitol, hexylene glycol, urea, or propylene glycol. Preferably, the formulation contains an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. Additional optional excipients include stabilizers, preservatives such as methylparaben, pH adjusting agents such as sodium hydroxide, chelating agents such as EDTA and its salts, and buffers.

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.

The formulation of the invention may be made by any method known to make a uniphase or multiphase pharmaceutical formulation for topical administration. In order to make a multiphase formulation such as an emulsion, for example, the components of the aqueous phase and of the oil phase may be separately combined and mixed until homogenous solutions are obtained and then the aqueous solution and the oil solution may be combined and mixed, such as by shear mixing, to form the formulation. The oil phase may be added to the water phase, or the water phase may be added to the oil phase. The phases may be combined and mixed, such as at elevated temperatures of 50-90°C or at room temperature, that is between 20-30°C, or at a temperature between room temperature and the elevated temperatures.

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The formulation may be used for topical treatment or prophylaxis of a dermatological or mucosal disorder that is responsive to the application of topical corticosteroids. Examples of such disorders include psoriasis, dermatitis such as atopic, contact, or hand dermatitis, eczema, and poison ivy dermatitis.

The concentration of the corticosteroid in the formulation is that which is sufficient to provide an anti-inflammatory response to an area of skin or mucous membrane to which it is applied. The concentration may vary depending on the particular disorder to be treated, the particular corticosteroid utilized, and other parameters.

Because the primary purpose to which the invention is conceived to pertain is to reduce the amount of corticosteroid that is available to enter the systemic circulation following the topical administration of corticosteroids, the preferred concentration of corticosteroid in the formulation of the invention is less than that present in prior art topical formulations containing the same corticosteroid. For example, both clobetasol propionate and halobetasol propionate topical formulations are presently available as creams and ointments in a concentration of 0.05% w/w. Thus, it is preferred that the concentration of such corticosteroid in the formulation of the present invention is less than 0.05% w/w. However, concentrations of corticosteroid at the same level, that is at 0.05%, or higher, are not excluded from the scope of the present invention unless indicated as such in the claims.

In a preferred embodiment, the formulation of the invention contains a concentration of the corticosteroid such as clobetasol propionate or halobetasol propionate that is 80% or less than that presently available, that is a concentration of 0.04% or less. In another preferred embodiment, the formulation contains a concentration of the corticosteroid

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that is 60% or less than that presently available, that is a concentration of 0.03% or less. In another preferred embodiment, the concentration is 50% or less than that presently available, that is a concentration is 0.025% or less. In another preferred embodiment, the formulation of the invention contains a concentration of corticosteroid that is 40% or less than that presently available, that is has a concentration of 0.02% or less. In another preferred embodiment, the formulation contains a concentration of the corticosteroid that is 20% or less than that presently available, that is has a concentration of 0.01% or less. In another preferred embodiment, the concentration of corticosteroid in the formulation of the invention is 10% or less than that presently available, that is 0.005% or less.

The concentration of the liquid oil component of the formulation containing a DCAE and/or an MCAE is at least that which is sufficient to dissolve at least 25% of the entire amount of the corticosteroid in the formulation at a room temperature of 22°C. In one embodiment, the concentration of the liquid oil component is sufficient to dissolve between 25% and 50% of the corticosteroid, such as about 40%. In a preferred embodiment, the concentration of the liquid oil component is sufficient to dissolve between 50% and 60% of the corticosteroid, such as about 55%. In another preferred embodiment, the concentration of the liquid oil component is sufficient to dissolve between 60% and 70% of the corticosteroid, such as about 65%. In another preferred embodiment, the concentration of the liquid oil component is sufficient to dissolve between 70% and 80% of the corticosteroid, such as about 75%. In another preferred embodiment, the concentration of the liquid oil component is sufficient to dissolve between 80% and 90% of the corticosteroid, such as about 85%. In another preferred embodiment, the concentration of the liquid oil component is

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sufficient to dissolve between 90% and 100% of the corticosteroid, such as about 95%.

In a more preferred embodiment, the concentration of the liquid oil component is sufficient to dissolve 100% or more of the corticosteroid in the formulation at a room temperature of 22°C. For example the concentration of the liquid oil component may be between 1.0 and 1.5 times that which is sufficient to dissolve the entire amount of the corticosteroid in the formulation. For example, the concentration of the liquid oil component may be greater than 1.5 times that which is sufficient to dissolve the entire amount of the corticosteroid in the formulation, such as between 1.5 times and 3.0 times that which is sufficient to dissolve the amount of corticosteroid in the formulation. For example, the concentration of the liquid oil component may be more than 3.0 times that which is sufficient to dissolve the entire amount of the corticosteroid in the formulation. Examples of suitable concentrations of liquid oil component in terms of amount required to dissolve the entire amount of corticosteroid in the formulation at room temperature include 0.25, 0.4, 0.5, 0.75, 1.0, 1.05, 1.15, 1.25, 1.25, 1.24, 1.45, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, and 6.0 times or higher than that which is sufficient to dissolve the corticosteroid in the formulation at a room temperature of 22°C.

The combined concentrations of the DCAE and/or the MCAE in the liquid oil component of the formulation is at least about 10% of the oil component, such as at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oil component. In one preferred embodiment, the DCAE, and MCAE if present, constitute 100% of the liquid oil component of the formulation.

The formulation of the invention maintains a VCA score as high or that is similar to the VCA score that is

obtained by the application of prior art formulations containing higher concentrations of the corticosteroid, such as the superpotent corticosteroid. Because the VCA score is determinative of local efficacy, the formulation of the invention, even at greatly reduced concentrations of corticosteroid, would be understood by one of skill in the art to be generally as effective locally in the skin as presently available formulations containing higher concentrations of corticosteroid. Additionally, because of the reduced concentration of corticosteroid in the formulation compared to that in the prior art compositions and the concomitant reduction in amount of corticosteroid that is available to enter the systemic circulation upon topical administration of the formulation, it is conceived that the formulation may have similar efficacy but improved safety compared to prior art formulations that contain higher concentrations of corticosteroid. Thus the formulations of this application have particular utility in infants and children in treating skin diseases such as atopic dermatitis and in both adults and children for treating recalcitrant or chronic skin diseases such as psoriasis. It is conceived that the present invention provides an equivalent or better efficacy in treating steroid responsive skin diseases compared to that produced by presently available topical formulations, and with potentially reduced local and systemic side effects.

The invention is further illustrated in the following non-limiting examples. In the examples, halobetasol propionate is utilized as an exemplary superpotent corticosteroid and diethyl sebacate is utilized as an exemplary dicarboxylic acid ester. It is understood, however, that halobetasol propionate is illustrative of the superpotent and potent corticosteroids, that diethyl sebacate is illustrative of the DCAE, and that isopropyl myristate is illustrative of the MCAE, and that any corticosteroid,

especially potent or superpotent corticosteroid, DCAE, or MCAE may be substituted for the illustrated halobetasol propionate, diethyl sebacate, and/or isopropyl myristate with similar results.

Example 1 - Formulations

The following formulations as shown in Table 1 were made containing the superpotent corticosteroid halobetasol as halobetasol propionate (HP). Formulations A to D are formulations of the invention. Formulation E is a formulation that is not within the scope of the present invention.

Formulation	A	B	C	D	E
Ingredients	% w/w				
Halobetasol Propionate (corticosteroid)	0.035	0.025	0.01	0.035	0.035
Diethyl Sebacate (DCAE)	3.0	2.1	0.8	0.9	
Isopropyl Myristate (MCAE)				11.0	
Light Mineral Oil	1.0	0.7	0.3		
Medium Chain Triglycerides					18.0
White Petrolatum					2.0
Butylated Hydroxytoluene					0.01
Sorbitan Monooleate	0.1	0.1	0.1	0.1	
Cholesterol					0.5
Stearyl Alcohol					1.0
Cetyl Alcohol					0.5
Propylene Glycol	7.5	7.5	7.5	7.5	7.5
Disodium Edetate Dihydrate	0.05	0.05	0.05	0.05	0.05
Pemulen® TR-1	0.40	0.40	0.40	0.40	0.40
Carbopol® 981	0.60	0.60	0.60	0.60	0.60
Methylparaben	0.17	0.17	0.17	0.17	0.17
Propylparaben	0.03	0.03	0.03	0.03	0.03
Sodium Hydroxide	q.s. pH 6.0 +/- 1				
Purified Water	q.s.ad 100				

Table 1

Example 2 - Determination of Saturation Solubility and Degree of Saturation

The saturation solubility of halobetasol propionate in each of formulations A to D of Example 1 was determined as follows. At a temperatures of 22° +/- 2°C, samples containing halobetasol in the liquid oil component components of

formulations A to D, respectively, were prepared and stored in glass vials. The samples were shaken at 395 to 405 oscillations/minute for approximately 72 hours using a Burrell WRIST-ACTION® Shaker Model 75 (Burrell Scientific, Pittsburgh, PA). Samples were then centrifuged for 40 minutes at 3500 rpm and the supernatant was collected. The supernatant was filtered using 0.45 µm PTFE ACRODISC® Pall syringe filter (Pall Corporation, Port Washington, NY). The filtered samples were analyzed by HPLC using a reverse phase column monitored at 254 nm UV detection. The degree of unsaturation of halobetasol propionate of each formulation was then calculated by multiplying the concentration (% w/w) of the liquid oil component by the saturation solubility of halobetasol in the liquid oil component components and dividing by the concentration of halobetasol propionate in the formulation. The data is shown below in Table 2.

Formulation	Concentration of Liquid Oil component (%w/w)	Saturation Solubility (%w/w)	Degree of Unsaturation
A	4	2.41	2.8
B	2.8	2.41	2.7
C	1.1	2.41	2.5
D	11.9	0.45	1.5

Table 2

Example 3 - Determination of VCA Scores

The mean VCA score of each of the formulations of Example 1 was determined as described in Dow, U.S. Patent No. 7,300,669 and was assigned a semi-quantitative subjective evaluation score on a scale of 0 to 4. The mean VCA score of a formulation corresponding to that of the commercial product Ultravate® 0.05%; NDC 0072-1400-50 (Bristol-Meyers Squibb Company, Princeton, NJ) was also determined. In contrast to the other formulations tested, Ultravate contains halobetasol propionate at a concentration of 0.05%. In determining the

mean VCA score, the evaluator was blinded as to the formulation being tested. The results are shown in Table 3.

Formulation	HP Conc (%w/w)	VCA Mean Score
A	0.035	2.37
B	0.025	2.40
C	0.010	2.47
D	0.035	2.43
E	0.035	1.77
Ultravate©	0.050	2.37

Table 3

As shown in Table 3, each of the formulations A to D of the present invention provided a VCA score similar to that of the prior art formulation Ultravate®. This high level of VCA score, which is indicative of the local desired response of the corticosteroid, was obtained even though the level of corticosteroid in the formulations of the invention are markedly lower than that in the prior art formulation. Formulation E, which contained the same concentration of corticosteroid as in Formulations A and D, had a markedly lower VCA score.

Example 4 - Lotion Formulations

Lotion formulations 4a and 4b of the present invention contain the ingredients shown in Table 4. These formulations may be made as follows.

A separate aqueous phase is made. In a manufacturing vessel, purified 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 is 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 propeller agitation Carbopol 981 and

Pemulen TR-1 are added to the mixture and dispersed. The propeller mixing is continued until the polymers are fully dispersed and hydrated.

A separate oil phase is made. In a vessel, diethyl sebacate and halobetasol propionate are combined. The mixture is agitated until a solution is achieved. With continuous propeller mixing, light mineral oil and sorbitan monooleate are added. Mixing is continued until a solution is obtained.

In a separate vessel, a 1N solution of sodium hydroxide is prepared.

With high speed rotor-stator mixing, the oil phase containing the drug (halobetasol propionate) is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Propeller mixing is then used in place of the high speed rotor-stator mixing. With continuous mixing an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5 ± 0.5. Propeller mixing is continued until a homogeneous lotion is obtained.

	% w/w	
Ingredients	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0 - 6.0	pH 4.0 - 6.0
Purified Water, q.s. ad	100	100

Table 4

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Example 5 - Stability Data

A lotion formulation was made by the method of Example 4 using the ingredients listed in Table 5.

Ingredients	Percent w/w
Halobetasol propionate (HP)	0.025
Diethyl Sebacate	2.10
Light Mineral Oil	0.70
Sorbitan Monooleate	0.10
Propylene Glycol	7.50
Methylparaben	0.17
Propylparaben	0.03
Edetate Disodium, Dihydrate	0.05
Pemulen TR-1	0.40
Carbopol 981	0.60
Sodium Hydroxide	q.s. ad pH 5.0
Purified Water	q.s. ad 100

Table 5

The formulation was packaged in glass screw-cap jars and tested for stability at refrigerator temperature (5°C), room temperature (25°C), and accelerated temperature (40°C) and tested at the beginning of the study and periodically for up to 6 months. Description was performed by visual observation, pH was measured with a calibrated pH meter, and viscosity was measured with a Brookfield rotational viscometer using spindle 27 and a speed of 12 rpm. The content of halobetasol propionate was determined by reverse phase HPLC using a C18 column and UV detection. The stability specifications for the halobetasol lotion that would be required for a commercial product would typically be as shown in Table 6.

PARAMETER	FDA REQUIREMENT
Description	no substantial change
pH	4.0 to 6.0
Viscosity	7,500 to 15,000 cps
HP Content	90 to 110% of labeled amount

Table 6

The physical and chemical stability test results for this formulation are indicated below in Table 7.

Condition	Time	Description	pH	Viscosity (cps)	HP Content (% of labeled amount)
Initial	0 months	White to off-White Lotion	5.1	10,833	99.4
5°C	6 months	Conforms	5.1	12,285	94.0
25°C	3 months		5.1	12,140	95.3
	6 months		5.1	13,215	92.1
40°C	1 months		5.1	12,090	95.1
	3 months		5.1	12,090	93.4
	6 months		5.1	12, 070	92.5

Table 7

The HP lotion was determined to be within the typical specifications at all test times. The data of Table 6 indicates that this lotion product would be expected to have a 2 year shelf life at room temperature based on the favorable results after 6 months at 40°C - the accelerated condition accepted by the Food and Drug Administration to support a 2 year product shelf life at room temperature.

Further modifications, uses, and applications of the invention described herein will be apparent to those skilled in the art. It is intended that such modifications be encompassed in the following claims.

Claims

1. A pharmaceutical composition for topical application to the skin of an individual comprising a corticosteroid selected from the group consisting of those listed on Table 1 of this specification at a concentration less than the lowest concentration indicated on Table 1 for the corticosteroid, and a liquid oil component comprising one or more esters of monocarboxylic and dicarboxylic acids, wherein at least 25% of the corticosteroid is solubilized in the liquid oil component at room temperature and wherein the concentration of the esters in the liquid oil component is at least 10% of the concentration of the liquid oil component in the composition.

2. The pharmaceutical composition of claim 1 wherein the corticosteroid is selected from the group consisting of clobetasol propionate, betamethasone dipropionate, halobetasol propionate, diflorasone diacetate, fluocinonide, and desoximetasone at a concentration less than 0.05%, or selected from the group consisting of beclomethasone and budesonide at a concentration less than 0.025%, or selected from the group consisting of mometasone furuoate and halcinonide at a concentration less than 0.1%.

3. The pharmaceutical composition of claim 2 wherein the corticosteroid is a corticosteroid selected from the group consisting of clobetasol propionate, betamethasone dipropionate, halobetasol propionate, and fluocinonide.

4. The pharmaceutical composition of any of claim 1 to 3 wherein the corticosteroid is corticosteroid selected from the group consisting of betamethasone dipropionate, mometasone

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furoate, diflorasone acetate, halcinonide, fluocinonide, and desoximetasone.

5. The pharmaceutical composition of any of claims 1 to 4 wherein the concentration of the corticosteroid is 0.025% or less.

6. The pharmaceutical composition of any of claims 1 to 4 wherein the concentration of the corticosteroid is 0.01% or less.

7. The pharmaceutical composition of any of claims 1 to 6 wherein the concentration of the liquid oil component is sufficient to dissolve the amount of corticosteroid in the composition at a temperature of 22 degrees C.

8. The pharmaceutical composition of claim 7 wherein the concentration of the liquid oil component is between 1.5 and 3 times that required to completely solubilize the amount of corticosteroid in the composition at a temperature of 22 degrees C.

9. The pharmaceutical composition of claim 8 wherein the concentration of the liquid oil component is between 1.75 and 2.75 times that required to completely solubilize the amount of corticosteroid in the composition at a temperature of 22 degrees C.

10. The pharmaceutical composition of any of claims 1 to 9 wherein the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component in the composition.

11. The pharmaceutical composition of claim 10 wherein the concentration of the esters in the liquid oil component is at least 50% of the concentration of the liquid oil component in the composition.

12. The pharmaceutical composition of claim 11 wherein the concentration of the esters in the liquid oil component is at least 70% of the concentration of the liquid oil component in the composition.

13. The pharmaceutical composition of claim 12 wherein the concentration of the esters in the liquid oil component is at least 90% of the concentration of the liquid oil component in the composition.

14. The pharmaceutical composition of claim 13 wherein the concentration of the esters in the liquid oil component is 100% of the concentration of the liquid oil component in the composition.

15. The pharmaceutical composition of any of claims 1 to 14 wherein the liquid oil component comprises a dicarboxylic acid ester.

16. The pharmaceutical composition of claim 15 wherein the dicarboxylic acid ester is diethyl sebacate.

17. The pharmaceutical composition of any of claims 1 to 16 wherein the liquid oil component comprises a monocarboxylic acid ester.

18. The pharmaceutical composition of claim 17 wherein the monocarboxylic acid ester is isopropyl myristate.

19. The pharmaceutical composition of claim 7 wherein the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component in the composition.

20. The pharmaceutical composition of claim 19 wherein the concentration of the esters in the liquid oil component is at least 50% of the concentration of the liquid oil component in the composition.

21. The pharmaceutical composition of claim 20 wherein the concentration of the esters in the liquid oil component is at least 70% of the concentration of the liquid oil component in the composition.

22. The pharmaceutical composition of claim 21 wherein the concentration of the esters in the liquid oil component is at least 90% of the concentration of the liquid oil component in the composition.

23. The pharmaceutical composition of claim 22 wherein the concentration of the esters in the liquid oil component is 100% of the concentration of the liquid oil component in the composition.

24. The pharmaceutical composition of claim 7 wherein the liquid oil component comprises a dicarboxylic acid ester.

25. The pharmaceutical composition of claim 7 wherein the liquid oil component comprises a monocarboxylic acid ester.

26. The pharmaceutical formulation of claim 1 wherein the corticosteroid is halobetasol propionate at a

concentration of 0.025% or less, the liquid oil component comprises diethyl sebacate, and wherein at least 50% of the corticosteroid is solubilized in the liquid oil component at room temperature.

27. The pharmaceutical formulation of claim 26 wherein the concentration of the liquid oil component is between 1.5 and 3 times that required to completely solubilize the amount of corticosteroid in the composition at a temperature of 22 degrees C.

28. The pharmaceutical composition of any of claims 1 or 4 to 25 wherein the corticosteroid is selected from the group consisting of fluticasone propionate at a concentration of less than 0.005%, fluocinolone acetonide at a concentration of less 0.01%, triamcinolone acetonide at a concentration of less than 0.025%, flurandernolide, desonide, and aclometasone dipropionate at a concentration of less than 0.05%, amcinonide, betamethasone valerate, prednicarbate, hydrocortisone butyrate, and hydrocortisone probutate at a concentration of less than 0.1%, and hydrocortisone valerate at a concentration of less than 0.2%.

29. The pharmaceutical composition of claim 28 wherein the corticosteroid is desonide.

30. A method for treating a disorder of the skin that is amenable to treatment with a topical corticosteroid comprising providing a pharmaceutical composition of any of claims 1 to 6 or 10 to 18 and applying an amount to the skin that is effective in ameliorating the signs or symptoms of the disorder.

31. A method for treating a disorder of the skin that is amenable to treatment with a topical corticosteroid comprising providing a pharmaceutical composition of claim 7 and applying an amount to the skin that is effective in ameliorating the signs or symptoms of the disorder.

32. A method for treating a disorder of the skin that is amenable to treatment with a topical corticosteroid comprising providing a pharmaceutical composition of claim 26 or 27 and applying an amount to the skin that is effective in ameliorating the signs or symptoms of the disorder.

33. A method for treating a disorder of the skin that is amenable to treatment with a topical corticosteroid comprising providing a pharmaceutical composition of claim 28 and applying an amount to the skin that is effective in ameliorating the signs or symptoms of the disorder.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/059861

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/56 (2012.01)
USPC - 514/163
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(8) - A61K 9/00, 9/06, 31/56 31/57, 31/573; A61P 17/00 (2012.01)
USPC - 424/78.02, 401; 514/18.6, 18.7, 159, 163, 169, 170, 171, 179, 180

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)
PatBase, Orbit.com, Proquest

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/039251 A1 (WEI et al) 08 April 2010 (08.04.2010) entire document	1-4, 26, 27, 32
Y	US 2005/0101582 A1 (LYONS et al) 12 May 2005 (12.05.2005) entire document	1-4, 26, 27, 32
Y	WO 2009/047788 A2 (DHUPPAD et al) 16 April 2009 (16.04.2009) entire document	1-4, 26, 27, 32
Y	US 2009/0012051 A1 (SUGISHITA et al) 08 January 2009 (08.01.2009) entire document	26, 27, 32
Y	US 4,370,322 A (BUSSE et al) 25 January 1983 (25.01.1983) entire document	27

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

* 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
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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
"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	Date of mailing of the international search report
16 February 2012 12 MAR 2012	
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/059861

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-25, 28-31, 33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

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WO 2012/061630 A2

(54) Title: COMPOSITION AND METHOD FOR TREATING SKIN CONDITIONS

(57) Abstract: Compositions and methods for treatment of conditions affecting skin and/or mucosal surfaces of a subject that make use of an imidazoquinoline compound and a retinoid agent are described.

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COMPOSITION AND METHOD FOR TREATING SKIN CONDITIONS

RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application Serial No. 61/410,110 filed November 4, 2010, the entire disclosure of which is incorporated herein by this reference.

TECHNICAL FIELD

[0002] The presently-disclosed subject matter relates to the field of medical dermatology, and more specifically to the treatment of skin conditions. In particular, the presently-disclosed subject matter relates to compositions and methods for treating skin conditions, including a combination of an imidazoquinoline compound, and a retinoid agent.

INTRODUCTION

[0003] Imidazoquinoline compounds are a family of compounds that have been shown to provide certain beneficial effects, including antiviral and antitumor effects. For example, imiquimod is an immune-modifying agent that, when administered topically to a subject, activates local toll-like receptors to increase interferon and thus the subject's immune response to cells that are over-proliferating due to infection with viral particles or a mutation in the p53 tumor suppressor oncogene. Imiquimod is commercially available as a 3.75% and a 5% cream. It was initially used for anogenital warts, and it has now been FDA-approved for actinic keratoses on the face and scalp, and for superficial basal cell carcinomas. It has

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also been used off-label for common warts, *molluscum contagiosum*, keloids, lentigo maligna, SCC *in situ*, and extramammary Paget's disease.

[0004] While treatment of various skin conditions using imiquimod has shown promise, its efficacy is limited. In some cases it proves ineffective because it is unable to effectively penetrate the skin. Indeed, imiquimod is not able to effectively penetrate hyperkeratinized (abnormal and normal) skin, and therefore has a limited ability to have a significant effect in areas where thicker skin is present, e.g., palms, soles, and scalp of a subject. Warts, for example, are often found in areas where thicker skin is present and where imiquimod has limited efficacy. As such, other less-desirable therapies are employed. Such therapies include use of liquid nitrogen, curettage, laser, cautery, etc. which result in significant pain and local destruction of involved and uninvolved tissue. In addition, very few topical therapies have demonstrated adequate benefit to be included as a primary therapy. Furthermore, beneficial effects from imiquimod can require lengthy treatment regimens, sometimes 12-16 weeks of treatment are required to achieve results with facial and genital lesions, which can be unsatisfactory from a treatment standpoint, and which can give rise to patient compliance obstacles.

[0005] Retinoid agents are a group of compounds that have been shown to have a variety of beneficial effects and have been used in a number of dermatologic products. For example, tazarotene is a retinoic acid derivative, which acts on the retinoic acid receptor within a cell of a subject to decrease cellular proliferation. Tazarotene is commercially available as a 0.05% and a 0.1% cream or gel. It is used in diseases of hyperkeratinization and epithelial cell proliferation, including pathologies such as acne and psoriasis.

[0006] Imidazoquinoline compounds and retinoid agents have been used independently for use in treating various skin conditions. Certain skin conditions have also been treated using alternating applications, at different points in time, e.g., application of imiquimod alone on day 1, and then application of tazarotene alone on day 2; however, such treatments have shown limited efficacy.

[0007] Imidazoquinoline compounds and retinoid agents are relatively difficult to formulate. Imiquimod, for example is well known to be a difficult compound to solubilize and therefore stability and compatibility issues have posed problems, not only for finding vehicles that allow imiquimod to be stably-maintained in a formulation for a relevant time period and/or at a relevant temperature, but packaging can even be a concern. Indeed, with regard to packaging, imiquimod formulations are often provided in sachets rather than tubes, because tubes cannot support stabile storage of many imiquimod formulations

[0008] An imidazoquinoline compound and a retinoid agent have not heretofore been administered simultaneously nor have they been combined and provided together in a single composition. Despite independent use of products, such as commercially-available imiquimod and commercially-available tazarotene, even for use by an individual in alternating applications at different points in time, there has never been a suggestion to combine the compounds into a single composition. Indeed, with the availability of imidazoquinoline compounds and retinoid agents in separate commercial products, and in view the notorious solubility challenges associated with imidazoquinoline compounds, which would call into question the ability to provide a compatible and stable composition including both an imidazoquinoline compound and a retinoid agent, there was no reason to attempt such a combination.

SUMMARY

[0009] The present inventor contemplated the simultaneous administration of an imidazoquinoline compound with a retinoid agent, such as by using a composition of the presently-disclosed subject matter. Such a composition was contemplated to achieve beneficial results as compared to the administration of an imidazoquinoline compound or a retinoid agent alone or in alternating treatments at different points in time. Without wishing to be bound by theory or mechanism, it is contemplated that the retinoid agent of the compositions disclosed herein, with the ability to normalize hyperkeratinization, can facilitate penetration of active agents delivered therewith. As further contemplated, an imidazoquinoline compound, such as imiquimod, has penetration limitations that can be overcome by co-administration with a retinoid agent.

[0010] As noted herein below, in providing a single composition including both an imidazoquinoline compound and a retinoid agent, unexpected and beneficial results are achieved. Beneficial results include increasing penetration of the imidazoquinoline compound component, which can increase the efficacy of the composition, and which can allow for treatment in locations and on lesions where imidazoquinoline compound and/or retinoid agent treatment was previously ineffective and/or resulted in undue or excessive irritation.

[0011] This Summary describes several embodiments of the presently-disclosed subject matter, and in many cases lists variations and permutations of these embodiments. This Summary is merely exemplary of the numerous and varied embodiments. Mention of one or

more representative features of a given embodiment is likewise exemplary. Such an embodiment can typically exist with or without the feature(s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this Summary or not. To avoid excessive repetition, this Summary does not list or suggest all possible combinations of such features.

[0012] The presently-disclosed subject matter includes compositions, pharmaceutical compositions, kits, and methods useful for treating conditions of the skin and/or mucosal surfaces of subjects. The composition of the presently-disclosed subject matter includes an imidazoquinoline compound; and a retinoid agent. Pharmaceutical compositions, methods, and kits of the presently-disclosed subject matter make use of the composition of the presently-disclosed subject matter.

[0013] In some embodiments, the imidazoquinoline compound is imiquimod, resiquimod, sotirimod, or mixtures thereof. In some embodiments, the imidazoquinoline compound is imiquimod. In some embodiments, the imidazoquinoline compound is resiquimod. In some embodiments, the imidazoquinoline compound is sotirimod. In some embodiments, the retinoid agent is selected from the group consisting of: retinol, retinal, retinyl acetate, retinaldehyde, retinyl palmitate, retinoic acid, retinyl propionate, retinyl linoleate, dehydroretinol, eretinate, eretrin, motretinide, tazarotene, isotretinoin, tretinoin, adapalene, bexarotene, fenretinide, and alitretinoin. In some embodiments, the retinoid agent is tazarotene. In some embodiments, the imidazoquinoline compound is selected from the group consisting of: imiquimod, resiquimod, and sotirimod; and the retinoid agent is selected from the group consisting of: retinol, retinal, retinyl acetate, retinaldehyde, retinyl palmitate, retinoic acid, retinyl propionate, retinyl linoleate, dehydroretinol, eretinate, eretrin, motretinide, tazarotene, isotretinoin, tretinoin, adapalene, bexarotene, fenretinide, and alitretinoin. In some embodiments, the imidazoquinoline compound is imiquimod and the retinoid agent is tazarotene.

[0014] In some embodiments, the composition further comprises additional ingredients. Such ingredients can include, for example, salicylic acid, urea, an alpha hydroxyl acid, and a beta hydroxyl acid. In some embodiments, the composition includes salicylic acid. In some embodiments, the composition includes urea. In some embodiments, the composition includes an alpha hydroxyl acid. In some embodiments, the composition includes a beta hydroxyl acid.

[0015] In some embodiments, the composition is provided for the treatment of a condition affecting the skin and/or mucosal surfaces of a subject.

[0016] In some embodiments, the composition is provided for the treatment of a condition affecting the skin of a subject. In some embodiments, the composition is provided for the treatment of a condition affecting the mucosal surfaces of a subject.

[0017] In some embodiments, the condition is selected from a wart, *molluscum contagiosum*, a keloid, and a skin cancer.

[0018] In some embodiments, the condition is a wart. In some embodiments, the wart is caused by a papillomavirus. In some embodiments, the wart is caused by a human papollomaviruses (HPV). In some embodiments, the wart is selected from: *verruca vulgaris* (common wart), *verruca plana* (flat wart) *condyloma acuminatum* or *verruca acuminate* (genital wart), and *verruca pedis* (plantar wart).

[0019] In some embodiments, the condition is *Molluscum contagiosum*.

[0020] In some embodiments, the condition is a keloid scar. In some embodiments, the condition is a hypertrophic scar.

[0021] In some embodiments, the condition is a skin cancer. In some embodiments, the skin cancer is a premalignant skin cancer. In some embodiments, the skin cancer is a malignant skin cancer. In some embodiments, the skin cancer is selected from melanoma and non-melanoma skin cancers, actinic keratoses, basal cell carcinomas, squamous cell carcinoma-in-situ or Bowen's disease, melanoma in-situ, and other unresectable carcinomas. In some embodiments, the skin cancer is actinic keratoses. In some embodiments, the skin cancer is a primary skin cancer. In some embodiments, the skin cancer is a secondary skin cancer. In some embodiments, the skin cancer is selected from : cutaneous T-cell lymphoma, extramammary Paget's disease, lentigo maligna, cutaneous melanoma metastases, and cutaneous leishmaniasis.

[0022] In some embodiments, the subject is a human. In some embodiments, the subject is a transplant patient. In some embodiments, the subject is receiving antirejection therapy following a transplant.

[0023] In some embodiments, the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). In some embodiments, the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). In some embodiments, the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.025% (wt/wt). In some embodiments, the retinoid agent is provided in the composition at a final concentration between about 0.5% (wt/wt) and about 0.01% (wt/wt).

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[0024] In some embodiments, the retinoid agent is tazarotene provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). In some embodiments, the tazarotene is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). In some embodiments, the tazarotene is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.025% (wt/wt). In some embodiments, the tazarotene is provided in the composition at a final concentration between about 0.5% (wt/wt) and about 0.01% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 1% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.5% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.1% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.05% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.01% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.005% (wt/wt). In some embodiments, the tazarotene is provided at a concentration of about 0.001% (wt/wt).

[0025] In some embodiments, the imidazoquinoline compound is provided in the composition at a final concentration between about 10% (wt/wt) and about 0.1% (wt/wt). In some embodiments, the imidazoquinoline compound is provided in the composition at a final concentration between about 7% (wt/wt) and about 3% (wt/wt).

[0026] In some embodiments, the imidazoquinoline compound is imiquimod provided in the composition at a final concentration between about 10% (wt/wt) and about 0.1% (wt/wt). In some embodiments, the imiquimod is provided in the composition at a final concentration between about 7% (wt/wt) and about 3% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 10% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 5% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 3.75% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 1% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 0.5% (wt/wt). In some embodiments, the imiquimod is provided at a concentration of about 0.1% (wt/wt).

[0027] In some embodiments, the composition allows for increased penetration of the imidazoquinoline compound. In some embodiments, the composition including a combination of the imidazoquinoline compound and the retinoid agent has a synergistic effect.

[0028] In some embodiments, the imidazoquinoline compound and the retinoid agent are provided in formulation that includes a solvent. In some embodiments, the solvent includes

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isostearic acid. In some embodiments, the solvent further includes alcohol, diethyl sebacate, or mineral oil.

[0029] In some embodiments, the composition is substantially stable at a temperature of 50°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable at a temperature of 40°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable at a temperature of 25°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable following up to three freeze/warm cycles from -20°C to 40°C.

[0030] In some embodiments, the composition is formulated for topical delivery. In some embodiments, the composition is formulated for intralesional injection.

[0031] As noted herein, the presently-disclosed subject matter includes pharmaceutical compositions of the composition described herein, including the compositions as described in this summary and throughout this application.

[0032] The presently-disclosed subject matter further includes a kit. Such kits include the compositions as described in this summary and throughout this application, and a device useful for administration of the composition. Such devices can include, for example, a stick, tape, an occlusive applicator, or an occlusive bandage.

[0033] The presently-disclosed subject matter further includes a method for the treatment of a condition affecting skin and/or a mucosal surface of a subject. Such methods include use of the compositions as described in this summary and throughout this application. The method includes administering an effective amount of the composition to the subject. In some embodiments, the composition is administered to an affected site on the skin and/or mucosal surface of the subject. In some embodiments, the composition is administered topically. In some embodiments, the composition is administered by intralegional injection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIGURE 1A is a picture of a wart on the heel of a subject prior to treatment using a composition of the presently-disclosed subject matter.

[0035] FIGURE 1B is a picture of the heel of the subject of FIGURE 1A following treatment using a composition of the presently-disclosed subject matter..

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[0036] FIGURE 2 is a bar graph showing cumulative penetration of Imiquimod following 24 hours of topical exposure in calculated ng/cm^2 penetrated based on a 5mg/cm^2 dose.

[0037] FIGURE 3 is a time course showing cumulative receptor phase levels of Imiquimod in calculated ng/cm^2 penetrated based on a 5mg/cm^2 dose.

[0038] FIGURE 4 is a bar graph showing dermal levels of Imiquimod following 24 hours of topical exposure in calculated ng/cm^2 Imiquimod based on a 5mg/cm^2 dose.

[0039] FIGURE 5 is a bar graph showing epidermal levels of Imiquimod following 24 hours of topical exposure in calculated ng/cm^2 Imiquimod based on a 5mg/cm^2 dose.

[0040] FIGURE 6 is a bar graph showing dermis plus receptor levels of Imiquimod following 24 hours of topical exposure in calculated ng/cm^2 Imiquimod based on a 5mg/cm^2 dose.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0041] The details of one or more embodiments of the presently-disclosed subject matter are set forth in this document. Modifications to embodiments described in this document, and other embodiments, will be evident to those of ordinary skill in the art after a study of the information provided in this document. The information provided in this document, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this document, including definitions, will control.

[0042] While the terms used herein are believed to be well understood by one of ordinary skill in the art, definitions are set forth to facilitate explanation of the presently-disclosed subject matter.

[0043] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the presently-disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently-disclosed subject matter, representative methods, devices, and materials are now described.

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[0044] Following long-standing patent law convention, the terms "a", "an", and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a cell" includes a plurality of such cells, and so forth.

[0045] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

[0046] As used herein, the term "about," when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments ±20%, in some embodiments ±10%, in some embodiments ±5%, in some embodiments ±1%, in some embodiments ±0.5%, and in some embodiments ±0.1% from the specified amount, as such variations are appropriate to perform the disclosed method.

[0047] As used herein, ranges can be expressed as from "about" one particular value, and/or to "about" another particular value. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units is also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0048] The presently-disclosed subject matter includes compositions and methods for using such compositions for the treatment of a condition affecting the skin and/or mucosal surfaces of a subject. Compositions of the presently-disclosed subject matter include an imidazoquinoline compound and a retinoid agent. In some embodiments, the compositions are pharmaceutical compositions. Methods of the presently-disclosed subject matter include administering an effective amount of a composition comprising an imidazoquinoline compound and a retinoid agent to a subject. The presently-disclosed subject matter includes use of the compositions disclosed herein for the treatment of a condition affecting the skin and/or mucosal surfaces of a subject.

[0049] The presently-disclosed subject matter overcomes problems associated with past formulations of imidazoquinoline compounds having limited efficacy. The presently-disclosed subject matter allows for the treatment of areas that before would have been too thick or unresponsive to an imidazoquinoline compound alone (or an imidazoquinoline

compound and a retinoid agent in alternating doses at different points in time). The presently-disclosed subject matter provides an alternative to destructive and painful therapies, e.g., liquid nitrogen, curettage, laser, cautery, surgical removal, etc. for certain skin conditions.

[0050] Furthermore, the composition of the presently-disclosed subject matter can be useful for treating a condition affecting the a mucosal surface of a subject. Heretofore, retinoids, such as tazarotene, have not typically been used on mucosal surfaces due to accompanying irritation. However, as described in the Examples, the compositions of the presently-disclosed subject matter have unexpected superior results that allow for efficacy at lower concentrations of tazarotene than have previously been used commercially. Such low concentrations decrease the likelihood of irritation to the subject such that embodiments of the compositions of the presently-disclosed subject matter are contemplated for use on mucosal surfaces such as the mouth or genitalia. For example, it is contemplated that a composition of the presently-disclosed subject matter could be provided in a cervical cap to treat a viral lesion, without the need to surgically treat the lesion. Surgical treatment of such lesions can involve removal of a portion of the cervix, resulting in severe consequences, such as a difficulty or an inability to maintain a pregnancy.

[0051] Without wishing to be bound by theory or mechanism, it is believe that the simultaneous administration of an imidazoquinoline compound and a retinoid agent in the composition described herein allows for increased penetration of the imidazoquinoline compound, thereby increasing the efficacy of the imidazoquinoline compound in locations and on lesions where it was previously ineffective or insufficiently effective. For example, the inability of imiquimod to penetrate hyperkeratinized (abnormal and normal) skin to the toll-like receptors of the dermis has limited its ability to have a significant effect in areas of where thicker skin is present, e.g., palms, soles, and scalp of a subject. Verrucae (warts) are often found on the palms, soles, and in periungual areas where imiquimod is of limited efficacy.

[0052] The term "increased penetration," as used herein with reference to penetration of an imidazoquinoline compound, refers to an increase that is affected by the combination of the imidazoquinoline compound with the retinoid agent in accordance with the presently-disclosed subject matter. As such, the increase refers to the penetration of the imidazoquinoline compound to a site of administration, e.g., lesion, when administered without concurrent administration of a retinoid agent, as compared to the penetration of the imidazoquinoline compound to a site of administration when the composition of the

presently-disclosed subject matter is administered. Penetration can be assessed, for example, using Franz diffusion cells, as described in the following references, all of which are incorporated herein by this reference: DePaula, Martins, and Bentley, "Development and validation of HPLC method for imiquimod determination in skin penetration studies," Biomed Chromatogr 22(12): 1416-23 (2008); Owens ML, Bridson WE, Smith SL, Myers JA, Fox TL, and Wells TM, "Percutaneous penetration of Aldara cream, 5% during the topical treatment of genital and perianal warts," Prim Care Update Ob Gyns. 5(4):151 (1998).

[0053] As used herein, the term "imidazoquinoline compound" is inclusive of imiquimod (1-(2-methylpropyl)-1H-imidpzo[4,5-c]quinolin-4-amine), resiquimod (4-amino-α, α -dimethyl-2-ethoxymethyl-1H-imidazo[4,5-c]quinoli- ne-1-ethanol), sotirimod (2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine), and analogs thereof. The term "imidazoquinoline compound" is further inclusive of other imidazoquinoline compounds and derivatives thereof known to those of ordinary skill in the art, including those described in Stanley (2002) Clin. Exp. Dermatol. 27(7):571-577; Jones (2003) Curr. Opin. Investig. Drugs 4(2):214-218; and U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,346,905; 5,395,937; 5,238,944; and 5,525,612; and U.S. Patent Application Publication Nos. 2008/0213308; 2009/0182004; 2009/0182005; 2011/0217323; 2011/0245289; and 2011/0250237, each of which is incorporated herein by reference. It is noted that imidazoquinoline compounds have utility as toll-like receptor agonists or activators, e.g., TLR-7. In some embodiments, of the presently-disclosed subject matter, compositions can include a toll-like receptor agonist and a retinoid agent. Imiquimod, a compound in the imidazoquinoline family has been shown to display both antiviral and antitumor effects (Diebold et al. "Innate antiviral responses by means of toll-like receptor (TLR)-7-mediated recognition of single-stranded RNA". Science 204;303: 1529-1531; Barnetson et al. "Imiquimod induced regression of clinically diagnosed superficial basal cell carcinoma is associated with early infiltration by CD4 T cells and dendritic cells". Clin. Exp. Dermatol 2004;29: 639-643).

[0054] Without wishing being bound by theory or mechanism, Imiquimod appears to act via TLR-7 (Hemmi et al. "Small anti-viral compounds activate immune cells via the TLR 7 MyD88-dependent signaling pathway". Nat. Immunol 2002; 3:196-200). Imiquimod can inhibit the progression of actinic keratosis (AK) into invasive skin cancer, usually squamous cell carcinoma (SCC). Although imiquimod does not appear to have direct antineoplastic activity (Schon et al. "Tumor-selective induction of apoptosis and the small-molecule

immune response modifier imiquimod." J Natl.Cancer Inst. 2003, 95:1138-49), it has shown efficacy against a variety of tumors, including skin tumors.

[0055] As used herein the term "retinoid agent" refers to compounds having the general structure of vitamin A (retinol) and variations of that structure having a similar biological and pharmacological activity as retinol. Examples of retinoids include, but are not limited to, retinol, retinal, retinyl acetate, retinaldehyde, retinyl palmitate, retinoic acid, retinyl propionate, retinyl linoleate, dehydroretinol, eretinate, eretrin, motretinide, tazarotene, isotretinoin, tretinoin, adapalene, bexarotene, fenretinide, and alitretinoin.

[0056] As will be recognized by one of ordinary skill in the art upon study of the present document, in some cases it could be desirable to include further ingredients in the composition as described herein. Examples of such further ingredients include, but are not limited to salicylic acid, urea, alpha-hydroxy acids, and beta-hydroxy acids. Those of ordinary skill in the art will immediately recognize that various additional ingredients can be beneficial to provide in certain embodiments of the claimed composition, e.g., vehicle enhancers such as propylene glycol.

[0057] Compositions of the presently-disclosed subject matter are useful for the treatment of various conditions affecting skin and mucosal surfaces (mouth and genetalia) of a subject. Such conditions include a wart, *molluscum contagiosum*, a keloid, and a skin cancer.

[0058] The term "wart" as used herein refers to a growth caused by a papillomavirus at any location on a subject, and is inclusive of, but not limited to, warts caused by human papollomaviruses (HPV), such as, *verruca vulgaris* (common wart), *verruca plana* (flat wart) *condyloma acuminatum* or *verruca acuminate* (genital wart), and *verruca pedis* (plantar wart).

[0059] *Molluscum contagiosum* is an infection caused by a group of viruses in the Pox-viridae family, known as mulluscum contagiosum viruses (MCV).

[0060] The term "keloid" as used herein is inclusive of a keloid scar resulting from an overgrowth of scar tissue that occurs at the site of a skin injury. Although the term keloid is used to refer to refer an overgrowth of a scar having a tendency to migrate beyond the boundaries of the original skin injury, and hypertrophic scar is a term used to refer to raised scars that do not so-migrate, as used herein, the term "keloid" is inclusive of both keloid scars and hypertrophic scars, both of which are characterized by an overgrowth of scar tissue, which can be accompanied by itching and pain.

[0061] As used herein, the term "skin cancer" is used to refer to malignant and premalignant skin cancers. As such, the term "skin cancer" is inclusive of melanoma and

non-melanoma skin cancers, actinic keratoses, basal cell carcinomas, squamous cell carcinoma-in-situ or Bowen's disease, melanoma in-situ, and other unresectable carcinomas. The term "skin cancer" refers to both primary and secondary cancers of the skin. In this regard, the term is inclusive of metastatic lesions caused by a primary skin cancer or another cancer that metastasizes to the skin. Further, the term includes the following nonlimiting examples: cutaneous T-cell lymphoma, extramammary Paget's disease, lentigo maligna, cutaneous melanoma metastases, and cutaneous leishmaniasis. See Jackson and Callen, (In Press) Chapter 128: Immunomodulators. In Bolognia, Jorizzo, and Rapini *Dermatology*, 3d. Edition, which is incorporated herein by this reference.

[0062] As used herein, the terms "treatment" or "treating" relate to any treatment of a condition affecting the skin and/or mucosal surface of a subject, including but not limited to prophylactic treatment and therapeutic treatment As such, the terms treatment or treating include, but are not limited to: inhibiting the progression of a condition; arresting or inhibiting the development of a condition; reducing the severity of a condition; ameliorating or relieving symptoms associated with a condition; and causing a regression of the condition or one or more of the symptoms associated with the condition. For example, treatment or treating can include, but are not limited to: reduction in size and in thickness and hyperkeratinization; reduced pain; reduced itching; reduced inflammation adjacent to, but not the actual treatment area (redness and swelling away from the zone of topical application); reduction in the number of lesions; reduction in the occurrence of new lesions, resolution of lesions beyond the treated area ("field effect"), and reduction in rates of remission, e.g., due to increased immune surveillance.

[0063] As used herein, the term "effective amount" refers to a dosage sufficient to provide treatment for the condition being treated. This can vary depending on the patient, the condition and the treatment being effected. The exact amount that is required will vary from subject to subject, depending on the species, age, and general condition of the subject, the particular carrier or adjuvant being used, mode of administration, and the like. As such, the effective amount will vary based on the particular circumstances, and an appropriate effective amount can be determined in a particular case by one of ordinary skill in the art using only routine experimentation.

[0064] As used herein, the term "subject" includes both human and animal subjects. Thus, veterinary therapeutic uses are provided in accordance with the presently disclosed subject matter. As such, the presently disclosed subject matter provides for the treatment of mammals such as humans and non-human primates, as well as those mammals of importance

due to being endangered, such as Siberian tigers; of economic importance, such as animals raised on farms for consumption by humans; and/or animals of social importance to humans, such as animals kept as pets or in zoos. Examples of such animals include but are not limited to: carnivores such as cats and dogs; swine, including pigs, hogs, and wild boars; ruminants and/or ungulates such as cattle, oxen, sheep, giraffes, deer, goats, bison, camels, and horses. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

[0065] Contemplated subjects include transplant patients, who can be at risk for developing a cancer, particularly after extended use of antirejection therapy. Such subjects can develop squamous cell carcinomas, for example, which tend to be more aggressive and which are a significant cause of death in these subjects. Compositions and methods of the presently-disclosed subject matter can be used for chemoprevention in such a transplant patient.

[0066] As proposed herein, including an imidazoquinoline compound and a retinoid agent in the same composition increases the efficacy of the components of the composition, as compared their efficacy when administered separately. In some embodiments, the increase in the efficacy is more than an additive effect, and combination of the imidazoquinoline compound and the retinoid agent can be described as having a synergistic effect.

[0067] As used herein, "synergy" and "synergistic effect" can refer to any substantial enhancement, in a composition of at least two compounds, of a measurable effect when compared with the effect of a component of the composition, e.g., one active compound alone. Measurable effects could include, for example, reduction in thickness and hyperkeratinization, reduced pain, inflammation adjacent to, but not the actual treatment area (redness and swelling away from the zone of topical application), fewer or reduction of new lesions demonstrating the immune recognition rather than simply local irritation, and resolution of verrucae beyond the treated area demonstrating a systemic recognition or "field effect"

[0068] Synergy is a specific feature of a blend of compounds, and is above any background level of enhancement that would be due solely to, e.g., additive effects of any random combination of ingredients. This combination has demonstrated clinically synergistic effects.

[0069] In some embodiments, a substantial enhancement of a measurable effect can be expressed as a coefficient of synergy. A coefficient of synergy is an expression of a comparison between measured effects of a composition and measured effects of a comparison

composition. The comparison composition can be a component of the composition, e.g., imiquimod. In some embodiments, the synergy coefficient can be adjusted for differences in concentration of the complete composition and the comparison composition.

[0070] Synergy coefficients can be calculated as follows. An activity ratio (R) can be calculated by dividing the % effect of the composition (AB) by the % effect of the comparison compound (X_n), as follows:

$$R = AB/X_n. \qquad \text{Formula 1}$$

[0071] A concentration adjustment factor (F) can be calculated based on the concentration (C_n), i.e., % (wt/wt) or % (vol/vol), of the comparison compound in the composition, as follows:

$$F = 100/C_n \qquad \text{Formula 2}$$

[0072] The synergy coefficient (S) can then be calculated by multiplying the activity ratio (R) and the concentration adjustment factor (F), as follows:

$$S = (R)(F) \qquad \text{Formula 3}$$

[0073] As such, the synergy coefficient (S) can also by calculated, as follows:

$$S = [(AB/X_n)(100)]/C_n \qquad \text{Formula 4}$$

[0074] In Formula 4, AB is expressed as % effect of the blend, X_n is expressed as % effect of the comparison compound (X_n), and C_n is expressed as % (wt/wt) or % (vol/vol) concentration of the comparison composition in the blend. Additional information related to calculating synergy coefficients can be found in the Examples set forth in this document.

[0075] In some embodiments, a coefficient of synergy of about 1.1, 1.2, 1.3, 1.4, or 1.5 can be substantial and commercially desirable. In other embodiments, the coefficient of synergy can be from about 1.6 to about 5, including but not limited to about 1.8, 2.0, 2.5, 3.0, 3.5, 4.0, and 4.5. In other embodiments, the coefficient of synergy can be from about 5 to 50, including but not limited to about 10, 15, 20, 25, 30, 35, 40, and 45. In other embodiments, the coefficient of synergy can be from about 50 to about 500, or more, including but not limited to about 50, 75, 100, 125, 150, 200, 250, 300, 350, 400, and 450. Any coefficient of

synergy above 500, 1000, or 5000 is also contemplated within embodiments of the compositions.

[0076] Given that a broad range of synergies can be found in various embodiments of the invention, it is expressly noted that a coefficient of synergy can be described as being "greater than" a given number and therefore not necessarily limited to being within the bounds of a range having a lower and an upper numerical limit. Likewise, in some embodiments of the invention, certain low synergy coefficients, or lower ends of ranges, are expressly excluded. Accordingly, in some embodiments, synergy can be expressed as being "greater than" a given number that constitutes a lower limit of synergy for such an embodiment. For example, in some embodiments, the synergy coefficient is equal to or greater than 25; in such an embodiment, all synergy coefficients below 25, even though substantial, are expressly excluded.

[0077] In some embodiments, synergy or synergistic effect associated with a composition can be determined using calculations similar to those described in Colby, S. R., "Calculating synergistic and antagonistic responses of herbicide combinations," Weeds (1967) 15:1, pp. 20-22, which is incorporated herein by this reference. In this regard, the following formula can be used to express an expected % effect (E) of a composition including two compounds, Compound X and Compound Y:

$$E = X + Y - (X*Y/100) \qquad \text{Formula 5}$$

[0078] In Formula 5, X is the measured actual % effect of Compound X in the composition, and Y is the measured actual % effect of Compound Y of the composition. The expected % effect (E) of the composition is then compared to a measured actual % effect (A) of the composition. If the actual % effect (A) that is measured differs from the expected % effect (E) as calculated by the formula, then the difference is due to an interaction of the compounds. Thus, the composition has synergy (a positive interaction of the compounds) when $A > E$. Further, there is a negative interaction (antagonism) when $A < E$.

[0079] As noted herein, and as known to those of ordinary skill in the art, imidazoquinoline compounds have notorious solubility challenges, calling into question the ability to provide a compatible and stable composition including both an imidazoquinoline compound and a retinoid agent. Despite such challenges, the present inventor contemplated the composition and it was surprisingly discovered that an imidazoquinoline compound and a retinoid agent could be formulated in a single composition with unexpectedly beneficial

properties (See the Examples for further details). Such beneficial properties include physical stability and chemical stability of the composition.

[0080] Stability is a specific feature of embodiments of the composition of the presently-disclosed subject matter. In some embodiments, the composition is substantially stable at a temperature up to about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55°C for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, , 34 or 35 days. In some embodiments, the composition is substantially stable at a temperature of 50°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable at a temperature of 40°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable at a temperature of 25°C for a period of four (4) weeks. In some embodiments, the composition is substantially stable following up to three freeze/warm cycles from -20°C to 40°C. As used herein, the term "substantially stable" can refer to physical and/or chemical stability. As will be recognized by those of ordinary skill in the art, the term "substantially stable" can refer to stability of the composition under certain conditions, relative to an initial composition (i.e., when a particular batch of the composition is initially prepared). In this regard, as will be recognized by those of ordinary skill in the art, one manner in which stability of a particular embodiment of the composition can be determined is as follows: preparing a batch of the embodiment of the composition, making an initial assessment of a sample of the composition (control sample), subjecting a sample of the composition to conditions of interest (e.g., storage at a particular temperature for a particular time period) (test sample), making an assessment of the test sample, and comparing the assessment of the control sample to the assessment of the test sample. In some cases, to assess stability, it can be desirable to measure and compare the amount of the imidazoquinoline compound and the amount of the retinoid agent in the control sample and in the test same. Calculations can be made to determine whether the amounts present in the test sample are 100% ± 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5, or 0.1% of the amount that is in the control sample.

[0081] In some embodiments, a composition is provided wherein the imidazoquinoline compound and the retinoid agent are provided in a particular ratio relative to one another. For example, in some embodiments the imiquimod and the retinoid agent are provided in a ratio of about 20:1 to about 1:20, wherein the ratio is a weight ratio. In some embodiments the imiquimod and the retinoid agent are provided in a ratio of about 20:1, 19:1, 18:1, 17:1,

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16:1, 15:1, 14:1, 13:1, 12:1, 11:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19, or 1:20.

[0082] In some embodiments, the imidazoquinoline compound is provided in the composition at a final concentration of between about 10% (wt/wt) and about 0.1% (wt/wt). In some embodiments, imidazoquinoline compound is provided at a final concentration of between about 7% and about 3% (wt/wt). In some embodiments, the imidazoquinoline compound is provided at a final concentration of about 10.00%, 9.99%, 9.98%, 9.97%, 9.96%, 9.95%, 9.94%, 9.93%, 9.92%, 9.91%, 9.90%, 9.89%, 9.88%, 9.87%, 9.86%, 9.85%, 9.84%, 9.83%, 9.82%, 9.81%, 9.80%, 9.79%, 9.78%, 9.77%, 9.76%, 9.75%, 9.74%, 9.73%, 9.72%, 9.71%, 9.70%, 9.69%, 9.68%, 9.67%, 9.66%, 9.65%, 9.64%, 9.63%, 9.62%, 9.61%, 9.60%, 9.59%, 9.58%, 9.57%, 9.56%, 9.55%, 9.54%, 9.53%, 9.52%, 9.51%, 9.50%, 9.49%, 9.48%, 9.47%, 9.46%, 9.45%, 9.44%, 9.43%, 9.42%, 9.41%, 9.40%, 9.39%, 9.38%, 9.37%, 9.36%, 9.35%, 9.34%, 9.33%, 9.32%, 9.31%, 9.30%, 9.29%, 9.28%, 9.27%, 9.26%, 9.25%, 9.24%, 9.23%, 9.22%, 9.21%, 9.20%, 9.19%, 9.18%, 9.17%, 9.16%, 9.15%, 9.14%, 9.13%, 9.12%, 9.11%, 9.10%, 9.09%, 9.08%, 9.07%, 9.06%, 9.05%, 9.04%, 9.03%, 9.02%, 9.01%, 9.00%, 8.99%, 8.98%, 8.97%, 8.96%, 8.95%, 8.94%, 8.93%, 8.92%, 8.91%, 8.90%, 8.89%, 8.88%, 8.87%, 8.86%, 8.85%, 8.84%, 8.83%, 8.82%, 8.81%, 8.80%, 8.79%, 8.78%, 8.77%, 8.76%, 8.75%, 8.74%, 8.73%, 8.72%, 8.71%, 8.70%, 8.69%, 8.68%, 8.67%, 8.66%, 8.65%, 8.64%, 8.63%, 8.62%, 8.61%, 8.60%, 8.59%, 8.58%, 8.57%, 8.56%, 8.55%, 8.54%, 8.53%, 8.52%, 8.51%, 8.50%, 8.49%, 8.48%, 8.47%, 8.46%, 8.45%, 8.44%, 8.43%, 8.42%, 8.41%, 8.40%, 8.39%, 8.38%, 8.37%, 8.36%, 8.35%, 8.34%, 8.33%, 8.32%, 8.31%, 8.30%, 8.29%, 8.28%, 8.27%, 8.26%, 8.25%, 8.24%, 8.23%, 8.22%, 8.21%, 8.20%, 8.19%, 8.18%, 8.17%, 8.16%, 8.15%, 8.14%, 8.13%, 8.12%, 8.11%, 8.10%, 8.09%, 8.08%, 8.07%, 8.06%, 8.05%, 8.04%, 8.03%, 8.02%, 8.01%, 8.00%, 7.99%, 7.98%, 7.97%, 7.96%, 7.95%, 7.94%, 7.93%, 7.92%, 7.91%, 7.90%, 7.89%, 7.88%, 7.87%, 7.86%, 7.85%, 7.84%, 7.83%, 7.82%, 7.81%, 7.80%, 7.79%, 7.78%, 7.77%, 7.76%, 7.75%, 7.74%, 7.73%, 7.72%, 7.71%, 7.70%, 7.69%, 7.68%, 7.67%, 7.66%, 7.65%, 7.64%, 7.63%, 7.62%, 7.61%, 7.60%, 7.59%, 7.58%, 7.57%, 7.56%, 7.55%, 7.54%, 7.53%, 7.52%, 7.51%, 7.50%, 7.49%, 7.48%, 7.47%, 7.46%, 7.45%, 7.44%, 7.43%, 7.42%, 7.41%, 7.40%, 7.39%, 7.38%, 7.37%, 7.36%, 7.35%, 7.34%, 7.33%, 7.32%, 7.31%, 7.30%, 7.29%, 7.28%, 7.27%, 7.26%, 7.25%, 7.24%, 7.23%, 7.22%, 7.21%, 7.20%, 7.19%, 7.18%, 7.17%, 7.16%, 7.15%, 7.14%, 7.13%, 7.12%, 7.11%, 7.10%, 7.09%, 7.08%, 7.07%, 7.06%, 7.05%, 7.04%, 7.03%, 7.02%, 7.01%, 7.00%, 6.99%, 6.98%, 6.97%, 6.96%, 6.95%, 6.94%, 6.93%, 6.92%, 6.91%, 6.90%, 6.89%, 6.88%, 6.87%, 6.86%, 6.85%, 6.84%, 6.83%, 6.82%, 6.81%, 6.80%, 6.79%, 6.78%, 6.77%, 6.76%, 6.75%, 6.74%, 6.73%,

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6.72%, 6.71%, 6.70%, 6.69%, 6.68%, 6.67%, 6.66%, 6.65%, 6.64%, 6.63%, 6.62%, 6.61%, 6.60%, 6.59%, 6.58%, 6.57%, 6.56%, 6.55%, 6.54%, 6.53%, 6.52%, 6.51%, 6.50%, 6.49%, 6.48%, 6.47%, 6.46%, 6.45%, 6.44%, 6.43%, 6.42%, 6.41%, 6.40%, 6.39%, 6.38%, 6.37%, 6.36%, 6.35%, 6.34%, 6.33%, 6.32%, 6.31%, 6.30%, 6.29%, 6.28%, 6.27%, 6.26%, 6.25%, 6.24%, 6.23%, 6.22%, 6.21%, 6.20%, 6.19%, 6.18%, 6.17%, 6.16%, 6.15%, 6.14%, 6.13%, 6.12%, 6.11%, 6.10%, 6.09%, 6.08%, 6.07%, 6.06%, 6.05%, 6.04%, 6.03%, 6.02%, 6.01%, 6.00%, 5.99%, 5.98%, 5.97%, 5.96%, 5.95%, 5.94%, 5.93%, 5.92%, 5.91%, 5.90%, 5.89%, 5.88%, 5.87%, 5.86%, 5.85%, 5.84%, 5.83%, 5.82%, 5.81%, 5.80%, 5.79%, 5.78%, 5.77%, 5.76%, 5.75%, 5.74%, 5.73%, 5.72%, 5.71%, 5.70%, 5.69%, 5.68%, 5.67%, 5.66%, 5.65%, 5.64%, 5.63%, 5.62%, 5.61%, 5.60%, 5.59%, 5.58%, 5.57%, 5.56%, 5.55%, 5.54%, 5.53%, 5.52%, 5.51%, 5.50%, 5.49%, 5.48%, 5.47%, 5.46%, 5.45%, 5.44%, 5.43%, 5.42%, 5.41%, 5.40%, 5.39%, 5.38%, 5.37%, 5.36%, 5.35%, 5.34%, 5.33%, 5.32%, 5.31%, 5.30%, 5.29%, 5.28%, 5.27%, 5.26%, 5.25%, 5.24%, 5.23%, 5.22%, 5.21%, 5.20%, 5.19%, 5.18%, 5.17%, 5.16%, 5.15%, 5.14%, 5.13%, 5.12%, 5.11%, 5.10%, 5.09%, 5.08%, 5.07%, 5.06%, 5.05%, 5.04%, 5.03%, 5.02%, 5.01%, 5.00%, 4.99%, 4.98%, 4.97%, 4.96%, 4.95%, 4.94%, 4.93%, 4.92%, 4.91%, 4.90%, 4.89%, 4.88%, 4.87%, 4.86%, 4.85%, 4.84%, 4.83%, 4.82%, 4.81%, 4.80%, 4.79%, 4.78%, 4.77%, 4.76%, 4.75%, 4.74%, 4.73%, 4.72%, 4.71%, 4.70%, 4.69%, 4.68%, 4.67%, 4.66%, 4.65%, 4.64%, 4.63%, 4.62%, 4.61%, 4.60%, 4.59%, 4.58%, 4.57%, 4.56%, 4.55%, 4.54%, 4.53%, 4.52%, 4.51%, 4.50%, 4.49%, 4.48%, 4.47%, 4.46%, 4.45%, 4.44%, 4.43%, 4.42%, 4.41%, 4.40%, 4.39%, 4.38%, 4.37%, 4.36%, 4.35%, 4.34%, 4.33%, 4.32%, 4.31%, 4.30%, 4.29%, 4.28%, 4.27%, 4.26%, 4.25%, 4.24%, 4.23%, 4.22%, 4.21%, 4.20%, 4.19%, 4.18%, 4.17%, 4.16%, 4.15%, 4.14%, 4.13%, 4.12%, 4.11%, 4.10%, 4.09%, 4.08%, 4.07%, 4.06%, 4.05%, 4.04%, 4.03%, 4.02%, 4.01%, 4.00%, 3.99%, 3.98%, 3.97%, 3.96%, 3.95%, 3.94%, 3.93%, 3.92%, 3.91%, 3.90%, 3.89%, 3.88%, 3.87%, 3.86%, 3.85%, 3.84%, 3.83%, 3.82%, 3.81%, 3.80%, 3.79%, 3.78%, 3.77%, 3.76%, 3.75%, 3.74%, 3.73%, 3.72%, 3.71%, 3.70%, 3.69%, 3.68%, 3.67%, 3.66%, 3.65%, 3.64%, 3.63%, 3.62%, 3.61%, 3.60%, 3.59%, 3.58%, 3.57%, 3.56%, 3.55%, 3.54%, 3.53%, 3.52%, 3.51%, 3.50%, 3.49%, 3.48%, 3.47%, 3.46%, 3.45%, 3.44%, 3.43%, 3.42%, 3.41%, 3.40%, 3.39%, 3.38%, 3.37%, 3.36%, 3.35%, 3.34%, 3.33%, 3.32%, 3.31%, 3.30%, 3.29%, 3.28%, 3.27%, 3.26%, 3.25%, 3.24%, 3.23%, 3.22%, 3.21%, 3.20%, 3.19%, 3.18%, 3.17%, 3.16%, 3.15%, 3.14%, 3.13%, 3.12%, 3.11%, 3.10%, 3.09%, 3.08%, 3.07%, 3.06%, 3.05%, 3.04%, 3.03%, 3.02%, 3.01%, 3.00%, 2.99%, 2.98%, 2.97%, 2.96%, 2.95%, 2.94%, 2.93%, 2.92%, 2.91%, 2.90%, 2.89%, 2.88%, 2.87%, 2.86%, 2.85%, 2.84%, 2.83%, 2.82%, 2.81%, 2.80%, 2.79%, 2.78%, 2.77%, 2.76%, 2.75%, 2.74%, 2.73%, 2.72%, 2.71%, 2.70%, 2.69%, 2.68%, 2.67%, 2.66%, 2.65%,

2.64%, 2.63%, 2.62%, 2.61%, 2.60%, 2.59%, 2.58%, 2.57%, 2.56%, 2.55%, 2.54%, 2.53%, 2.52%, 2.51%, 2.50%, 2.49%, 2.48%, 2.47%, 2.46%, 2.45%, 2.44%, 2.43%, 2.42%, 2.41%, 2.40%, 2.39%, 2.38%, 2.37%, 2.36%, 2.35%, 2.34%, 2.33%, 2.32%, 2.31%, 2.30%, 2.29%, 2.28%, 2.27%, 2.26%, 2.25%, 2.24%, 2.23%, 2.22%, 2.21%, 2.20%, 2.19%, 2.18%, 2.17%, 2.16%, 2.15%, 2.14%, 2.13%, 2.12%, 2.11%, 2.10%, 2.09%, 2.08%, 2.07%, 2.06%, 2.05%, 2.04%, 2.03%, 2.02%, 2.01%, 2.00%, 1.99%, 1.98%, 1.97%, 1.96%, 1.95%, 1.94%, 1.93%, 1.92%, 1.91%, 1.90%, 1.89%, 1.88%, 1.87%, 1.86%, 1.85%, 1.84%, 1.83%, 1.82%, 1.81%, 1.80%, 1.79%, 1.78%, 1.77%, 1.76%, 1.75%, 1.74%, 1.73%, 1.72%, 1.71%, 1.70%, 1.69%, 1.68%, 1.67%, 1.66%, 1.65%, 1.64%, 1.63%, 1.62%, 1.61%, 1.60%, 1.59%, 1.58%, 1.57%, 1.56%, 1.55%, 1.54%, 1.53%, 1.52%, 1.51%, 1.50%, 1.49%, 1.48%, 1.47%, 1.46%, 1.45%, 1.44%, 1.43%, 1.42%, 1.41%, 1.40%, 1.39%, 1.38%, 1.37%, 1.36%, 1.35%, 1.34%, 1.33%, 1.32%, 1.31%, 1.30%, 1.29%, 1.28%, 1.27%, 1.26%, 1.25%, 1.24%, 1.23%, 1.22%, 1.21%, 1.20%, 1.19%, 1.18%, 1.17%, 1.16%, 1.15%, 1.14%, 1.13%, 1.12%, 1.11%, 1.10%, 1.09%, 1.08%, 1.07%, 1.06%, 1.05%, 1.04%, 1.03%, 1.02%, 1.01%, 1.00%, 0.99%, 0.98%, 0.97%, 0.96%, 0.95%, 0.94%, 0.93%, 0.92%, 0.91%, 0.90%, 0.89%, 0.88%, 0.87%, 0.86%, 0.85%, 0.84%, 0.83%, 0.82%, 0.81%, 0.80%, 0.79%, 0.78%, 0.77%, 0.76%, 0.75%, 0.74%, 0.73%, 0.72%, 0.71%, 0.70%, 0.69%, 0.68%, 0.67%, 0.66%, 0.65%, 0.64%, 0.63%, 0.62%, 0.61%, 0.60%, 0.59%, 0.58%, 0.57%, 0.56%, 0.55%, 0.54%, 0.53%, 0.52%, 0.51%, 0.50%, 0.49%, 0.48%, 0.47%, 0.46%, 0.45%, 0.44%, 0.43%, 0.42%, 0.41%, 0.40%, 0.39%, 0.38%, 0.37%, 0.36%, 0.35%, 0.34%, 0.33%, 0.32%, 0.31%, 0.30%, 0.29%, 0.28%, 0.27%, 0.26%, 0.25%, 0.24%, 0.23%, 0.22%, 0.21%, 0.20%, 0.19%, 0.18%, 0.17%, 0.16%, 0.15%, 0.14%, 0.13%, 0.12%, 0.11%, or 0.10% (wt/wt). In some embodiments, the imidazoquinoline compound is provided at a final concentration as recited in this paragraph, and is selected from imiquimod, resiquimod, and sotirimod. In some embodiments, the imidazoquinoline compound is imiquimod, which provided at a final concentration as recited in this paragraph. In some embodiments, the imidazoquinoline compound is resiquimod, which provided at a final concentration as recited in this paragraph. In some embodiments, the imidazoquinoline compound is sotirimod, which provided at a final concentration as recited in this paragraph.

[0083] In some embodiments, the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). In some embodiments, the retinoid agent is provided at a final concentration between about 1% (wt/wt) and about 0.025% (wt/wt). In some embodiments, the retinoid agent is provided at a concentration between about 0.5% (wt/wt) and about 0.01% (wt/wt). In some embodiments, the retinoid agent is provided at a final concentration of about 1.000%, 0.999%, 0.998%, 0.997%,

0.996%, 0.995%, 0.994%, 0.993%, 0.992%, 0.991%, 0.990%, 0.989%, 0.988%, 0.987%, 0.986%, 0.985%, 0.984%, 0.983%, 0.982%, 0.981%, 0.980%, 0.979%, 0.978%, 0.977%, 0.976%, 0.975%, 0.974%, 0.973%, 0.972%, 0.971%, 0.970%, 0.969%, 0.968%, 0.967%, 0.966%, 0.965%, 0.964%, 0.963%, 0.962%, 0.961%, 0.960%, 0.959%, 0.958%, 0.957%, 0.956%, 0.955%, 0.954%, 0.953%, 0.952%, 0.951%, 0.950%, 0.949%, 0.948%, 0.947%, 0.946%, 0.945%, 0.944%, 0.943%, 0.942%, 0.941%, 0.940%, 0.939%, 0.938%, 0.937%, 0.936%, 0.935%, 0.934%, 0.933%, 0.932%, 0.931%, 0.930%, 0.929%, 0.928%, 0.927%, 0.926%, 0.925%, 0.924%, 0.923%, 0.922%, 0.921%, 0.920%, 0.919%, 0.918%, 0.917%, 0.916%, 0.915%, 0.914%, 0.913%, 0.912%, 0.911%, 0.910%, 0.909%, 0.908%, 0.907%, 0.906%, 0.905%, 0.904%, 0.903%, 0.902%, 0.901%, 0.900%, 0.899%, 0.898%, 0.897%, 0.896%, 0.895%, 0.894%, 0.893%, 0.892%, 0.891%, 0.890%, 0.889%, 0.888%, 0.887%, 0.886%, 0.885%, 0.884%, 0.883%, 0.882%, 0.881%, 0.880%, 0.879%, 0.878%, 0.877%, 0.876%, 0.875%, 0.874%, 0.873%, 0.872%, 0.871%, 0.870%, 0.869%, 0.868%, 0.867%, 0.866%, 0.865%, 0.864%, 0.863%, 0.862%, 0.861%, 0.860%, 0.859%, 0.858%, 0.857%, 0.856%, 0.855%, 0.854%, 0.853%, 0.852%, 0.851%, 0.850%, 0.849%, 0.848%, 0.847%, 0.846%, 0.845%, 0.844%, 0.843%, 0.842%, 0.841%, 0.840%, 0.839%, 0.838%, 0.837%, 0.836%, 0.835%, 0.834%, 0.833%, 0.832%, 0.831%, 0.830%, 0.829%, 0.828%, 0.827%, 0.826%, 0.825%, 0.824%, 0.823%, 0.822%, 0.821%, 0.820%, 0.819%, 0.818%, 0.817%, 0.816%, 0.815%, 0.814%, 0.813%, 0.812%, 0.811%, 0.810%, 0.809%, 0.808%, 0.807%, 0.806%, 0.805%, 0.804%, 0.803%, 0.802%, 0.801%, 0.800%, 0.799%, 0.798%, 0.797%, 0.796%, 0.795%, 0.794%, 0.793%, 0.792%, 0.791%, 0.790%, 0.789%, 0.788%, 0.787%, 0.786%, 0.785%, 0.784%, 0.783%, 0.782%, 0.781%, 0.780%, 0.779%, 0.778%, 0.777%, 0.776%, 0.775%, 0.774%, 0.773%, 0.772%, 0.771%, 0.770%, 0.769%, 0.768%, 0.767%, 0.766%, 0.765%, 0.764%, 0.763%, 0.762%, 0.761%, 0.760%, 0.759%, 0.758%, 0.757%, 0.756%, 0.755%, 0.754%, 0.753%, 0.752%, 0.751%, 0.750%, 0.749%, 0.748%, 0.747%, 0.746%, 0.745%, 0.744%, 0.743%, 0.742%, 0.741%, 0.740%, 0.739%, 0.738%, 0.737%, 0.736%, 0.735%, 0.734%, 0.733%, 0.732%, 0.731%, 0.730%, 0.729%, 0.728%, 0.727%, 0.726%, 0.725%, 0.724%, 0.723%, 0.722%, 0.721%, 0.720%, 0.719%, 0.718%, 0.717%, 0.716%, 0.715%, 0.714%, 0.713%, 0.712%, 0.711%, 0.710%, 0.709%, 0.708%, 0.707%, 0.706%, 0.705%, 0.704%, 0.703%, 0.702%, 0.701%, 0.700%, 0.699%, 0.698%, 0.697%, 0.696%, 0.695%, 0.694%, 0.693%, 0.692%, 0.691%, 0.690%, 0.689%, 0.688%, 0.687%, 0.686%, 0.685%, 0.684%, 0.683%, 0.682%, 0.681%, 0.680%, 0.679%, 0.678%, 0.677%, 0.676%, 0.675%, 0.674%, 0.673%, 0.672%, 0.671%, 0.670%, 0.669%, 0.668%, 0.667%, 0.666%, 0.665%, 0.664%, 0.663%, 0.662%, 0.661%, 0.660%, 0.659%, 0.658%, 0.657%,

0.656%, 0.655%, 0.654%, 0.653%, 0.652%, 0.651%, 0.650%, 0.649%, 0.648%, 0.647%, 0.646%, 0.645%, 0.644%, 0.643%, 0.642%, 0.641%, 0.640%, 0.639%, 0.638%, 0.637%, 0.636%, 0.635%, 0.634%, 0.633%, 0.632%, 0.631%, 0.630%, 0.629%, 0.628%, 0.627%, 0.626%, 0.625%, 0.624%, 0.623%, 0.622%, 0.621%, 0.620%, 0.619%, 0.618%, 0.617%, 0.616%, 0.615%, 0.614%, 0.613%, 0.612%, 0.611%, 0.610%, 0.609%, 0.608%, 0.607%, 0.606%, 0.605%, 0.604%, 0.603%, 0.602%, 0.601%, 0.600%, 0.599%, 0.598%, 0.597%, 0.596%, 0.595%, 0.594%, 0.593%, 0.592%, 0.591%, 0.590%, 0.589%, 0.588%, 0.587%, 0.586%, 0.585%, 0.584%, 0.583%, 0.582%, 0.581%, 0.580%, 0.579%, 0.578%, 0.577%, 0.576%, 0.575%, 0.574%, 0.573%, 0.572%, 0.571%, 0.570%, 0.569%, 0.568%, 0.567%, 0.566%, 0.565%, 0.564%, 0.563%, 0.562%, 0.561%, 0.560%, 0.559%, 0.558%, 0.557%, 0.556%, 0.555%, 0.554%, 0.553%, 0.552%, 0.551%, 0.550%, 0.549%, 0.548%, 0.547%, 0.546%, 0.545%, 0.544%, 0.543%, 0.542%, 0.541%, 0.540%, 0.539%, 0.538%, 0.537%, 0.536%, 0.535%, 0.534%, 0.533%, 0.532%, 0.531%, 0.530%, 0.529%, 0.528%, 0.527%, 0.526%, 0.525%, 0.524%, 0.523%, 0.522%, 0.521%, 0.520%, 0.519%, 0.518%, 0.517%, 0.516%, 0.515%, 0.514%, 0.513%, 0.512%, 0.511%, 0.510%, 0.509%, 0.508%, 0.507%, 0.506%, 0.505%, 0.504%, 0.503%, 0.502%, 0.501%, 0.500%, 0.499%, 0.498%, 0.497%, 0.496%, 0.495%, 0.494%, 0.493%, 0.492%, 0.491%, 0.490%, 0.489%, 0.488%, 0.487%, 0.486%, 0.485%, 0.484%, 0.483%, 0.482%, 0.481%, 0.480%, 0.479%, 0.478%, 0.477%, 0.476%, 0.475%, 0.474%, 0.473%, 0.472%, 0.471%, 0.470%, 0.469%, 0.468%, 0.467%, 0.466%, 0.465%, 0.464%, 0.463%, 0.462%, 0.461%, 0.460%, 0.459%, 0.458%, 0.457%, 0.456%, 0.455%, 0.454%, 0.453%, 0.452%, 0.451%, 0.450%, 0.449%, 0.448%, 0.447%, 0.446%, 0.445%, 0.444%, 0.443%, 0.442%, 0.441%, 0.440%, 0.439%, 0.438%, 0.437%, 0.436%, 0.435%, 0.434%, 0.433%, 0.432%, 0.431%, 0.430%, 0.429%, 0.428%, 0.427%, 0.426%, 0.425%, 0.424%, 0.423%, 0.422%, 0.421%, 0.420%, 0.419%, 0.418%, 0.417%, 0.416%, 0.415%, 0.414%, 0.413%, 0.412%, 0.411%, 0.410%, 0.409%, 0.408%, 0.407%, 0.406%, 0.405%, 0.404%, 0.403%, 0.402%, 0.401%, 0.400%, 0.399%, 0.398%, 0.397%, 0.396%, 0.395%, 0.394%, 0.393%, 0.392%, 0.391%, 0.390%, 0.389%, 0.388%, 0.387%, 0.386%, 0.385%, 0.384%, 0.383%, 0.382%, 0.381%, 0.380%, 0.379%, 0.378%, 0.377%, 0.376%, 0.375%, 0.374%, 0.373%, 0.372%, 0.371%, 0.370%, 0.369%, 0.368%, 0.367%, 0.366%, 0.365%, 0.364%, 0.363%, 0.362%, 0.361%, 0.360%, 0.359%, 0.358%, 0.357%, 0.356%, 0.355%, 0.354%, 0.353%, 0.352%, 0.351%, 0.350%, 0.349%, 0.348%, 0.347%, 0.346%, 0.345%, 0.344%, 0.343%, 0.342%, 0.341%, 0.340%, 0.339%, 0.338%, 0.337%, 0.336%, 0.335%, 0.334%, 0.333%, 0.332%, 0.331%, 0.330%, 0.329%, 0.328%, 0.327%, 0.326%, 0.325%, 0.324%, 0.323%, 0.322%, 0.321%, 0.320%, 0.319%, 0.318%, 0.317%,

0.316%, 0.315%, 0.314%, 0.313%, 0.312%, 0.311%, 0.310%, 0.309%, 0.308%, 0.307%, 0.306%, 0.305%, 0.304%, 0.303%, 0.302%, 0.301%, 0.300%, 0.299%, 0.298%, 0.297%, 0.296%, 0.295%, 0.294%, 0.293%, 0.292%, 0.291%, 0.290%, 0.289%, 0.288%, 0.287%, 0.286%, 0.285%, 0.284%, 0.283%, 0.282%, 0.281%, 0.280%, 0.279%, 0.278%, 0.277%, 0.276%, 0.275%, 0.274%, 0.273%, 0.272%, 0.271%, 0.270%, 0.269%, 0.268%, 0.267%, 0.266%, 0.265%, 0.264%, 0.263%, 0.262%, 0.261%, 0.260%, 0.259%, 0.258%, 0.257%, 0.256%, 0.255%, 0.254%, 0.253%, 0.252%, 0.251%, 0.250%, 0.249%, 0.248%, 0.247%, 0.246%, 0.245%, 0.244%, 0.243%, 0.242%, 0.241%, 0.240%, 0.239%, 0.238%, 0.237%, 0.236%, 0.235%, 0.234%, 0.233%, 0.232%, 0.231%, 0.230%, 0.229%, 0.228%, 0.227%, 0.226%, 0.225%, 0.224%, 0.223%, 0.222%, 0.221%, 0.220%, 0.219%, 0.218%, 0.217%, 0.216%, 0.215%, 0.214%, 0.213%, 0.212%, 0.211%, 0.210%, 0.209%, 0.208%, 0.207%, 0.206%, 0.205%, 0.204%, 0.203%, 0.202%, 0.201%, 0.200%, 0.199%, 0.198%, 0.197%, 0.196%, 0.195%, 0.194%, 0.193%, 0.192%, 0.191%, 0.190%, 0.189%, 0.188%, 0.187%, 0.186%, 0.185%, 0.184%, 0.183%, 0.182%, 0.181%, 0.180%, 0.179%, 0.178%, 0.177%, 0.176%, 0.175%, 0.174%, 0.173%, 0.172%, 0.171%, 0.170%, 0.169%, 0.168%, 0.167%, 0.166%, 0.165%, 0.164%, 0.163%, 0.162%, 0.161%, 0.160%, 0.159%, 0.158%, 0.157%, 0.156%, 0.155%, 0.154%, 0.153%, 0.152%, 0.151%, 0.150%, 0.149%, 0.148%, 0.147%, 0.146%, 0.145%, 0.144%, 0.143%, 0.142%, 0.141%, 0.140%, 0.139%, 0.138%, 0.137%, 0.136%, 0.135%, 0.134%, 0.133%, 0.132%, 0.131%, 0.130%, 0.129%, 0.128%, 0.127%, 0.126%, 0.125%, 0.124%, 0.123%, 0.122%, 0.121%, 0.120%, 0.119%, 0.118%, 0.117%, 0.116%, 0.115%, 0.114%, 0.113%, 0.112%, 0.111%, 0.110%, 0.109%, 0.108%, 0.107%, 0.106%, 0.105%, 0.104%, 0.103%, 0.102%, 0.101%, 0.100%, 0.099%, 0.098%, 0.097%, 0.096%, 0.095%, 0.094%, 0.093%, 0.092%, 0.091%, 0.090%, 0.089%, 0.088%, 0.087%, 0.086%, 0.085%, 0.084%, 0.083%, 0.082%, 0.081%, 0.080%, 0.079%, 0.078%, 0.077%, 0.076%, 0.075%, 0.074%, 0.073%, 0.072%, 0.071%, 0.070%, 0.069%, 0.068%, 0.067%, 0.066%, 0.065%, 0.064%, 0.063%, 0.062%, 0.061%, 0.060%, 0.059%, 0.058%, 0.057%, 0.056%, 0.055%, 0.054%, 0.053%, 0.052%, 0.051%, 0.050%, 0.049%, 0.048%, 0.047%, 0.046%, 0.045%, 0.044%, 0.043%, 0.042%, 0.041%, 0.040%, 0.039%, 0.038%, 0.037%, 0.036%, 0.035%, 0.034%, 0.033%, 0.032%, 0.031%, 0.030%, 0.029%, 0.028%, 0.027%, 0.026%, 0.025%, 0.024%, 0.023%, 0.022%, 0.021%, 0.020%, 0.019%, 0.018%, 0.017%, 0.016%, 0.015%, 0.014%, 0.013%, 0.012%, 0.011%, 0.010%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, or 0.001% (wt/wt). In some embodiments, the retinoid agent is provided at a final concentration as recited in this paragraph, and is selected from retinol, retinal, retinyl acetate, retinaldehyde, retinyl palmitate, retinoic acid, retinyl

propionate, retinyl linoleate, dehydroretinol, eretinate, eretrin, motretinide, tazarotene, isotretinoin, tretinoin, adapalene, bexarotene, fenretinide, and alitretinoin. In some embodiments, the retinoid agent is retinol, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinal, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinyl acetate, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinaldehyde, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinyl palmitate, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinoic acid, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinyl propionate, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is retinyl linoleate, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is dehydroretinol, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is eretinate, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is eretrin, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is motretinide, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is tazarotene, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is isotretinoin, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is tretinoin, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is adapalene, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is bexarotene, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is fenretinide, which provided at a final concentration as recited in this paragraph. In some embodiments, the retinoid agent is alitretinoin, which provided at a final concentration as recited in this paragraph.

[0084] As noted herein, it will be recognized by one of ordinary skill in the art upon study of the present document that in some cases it could be desirable to include further ingredients in the composition as described herein, e.g., salicylic acid, urea, alpha-hydroxy acids, beta-hydroxy acids.

[0085] For example, in some embodiments, the composition can additionally include salicylic acid. In some embodiments, the salicylic acid is provided in a final concentration of about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 35, 40, 45, 50, 55, 60, 65, or 70% (wt/wt). Without wishing to be bound by theory or mechanism, the addition of salicylic acid can further increase the efficacy of some embodiments. The salicylic acid can result in epidermal desquamation of the hyperkeratosis, such that penetration of the composition is increased. It can also dilute or reduce the concentration of the retinoid agent, by altering the ratio of retinoid agent to imidazoquinoline compound (e.g., 5:1, 10:1, 20:1) so as to increase local tolerability and while maintaining efficacy.

[0086] For another example, in some embodiments, the composition can additionally include urea. In some embodiments, the urea is provided in a final concentration of about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 35, 40, 45, 50, 55, 60, 65, or 70% (wt/wt). Without wishing to be bound by theory or mechanism, the addition of urea can further increase the efficacy of some embodiments. The urea can result in increased penetration. It can also dilute or reduce the concentration of the retinoid agent, by altering the ratio of retinoid agent to imidazoquinoline compound (e.g., 5:1, 10:1, 20:1) so as to increase local tolerability and while maintaining efficacy.

[0087] For another example, in some embodiments, the composition can additionally include alpha-hydroxy acid. In some embodiments, the alpha-hydroxy acid is provided in a final concentration of about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 35, 40, 45, 50, 55, 60, 65, or 70% (wt/wt). Without wishing to be bound by theory or mechanism, the addition of alpha-hydroxy acid can further increase the efficacy of some embodiments. The alpha-hydroxy acid can result in epidermal desquamation of the hyperkeratosis, such that penetration of the composition is increased. It can also dilute or reduce the concentration of the retinoid agent, by altering the ratio of retinoid agent to imidazoquinoline compound (e.g., 5:1, 10:1, 20:1) so as to increase local tolerability and while maintaining efficacy.

[0088] For another example, in some embodiments, the composition can additionally include beta-hydroxy acid. In some embodiments, the beta-hydroxy acid is provided in a final concentration of about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 35, 40, 45, 50, 55, 60, 65, or 70% (wt/wt). Without wishing to be bound by theory or mechanism, the addition of beta-hydroxy acid can further increase the efficacy of some embodiments. The beta-hydroxy acid can result in epidermal desquamation of the hyperkeratosis, such that penetration of the composition is increased. It can also dilute or reduce the concentration of the retinoid agent,

by altering the ratio of retinoid agent to imidazoquinoline compound (e.g., 5:1, 10:1, 20:1) so as to increase local tolerability and while maintaining efficacy.

[0089] As will be apparent to one of ordinary skill in the art, further ingredients, such as vehicle enhancers can be provided in the composition of the presently-disclosed subject matter. Examples include, but are not limited to propylene glycol, cocamidopropyl betaine, oleamidoproplyl dimethylamine, propyl gallate, polyethylene glycol, and the like. Reference is also made to U.S. Patent Application Publication No. 2009/0182004, entitled "Imiquimod Formulation," which is incorporated herein by this reference.

[0090] In some embodiments, the composition is formulated for topical administration. In some embodiments, the composition can include a concentration of each active ingredient from about 1 to 30% in a carrier such as a pharmaceutical cream or gel base. Various formulations for topical use include, but are not limited to, drops, tinctures, lotions, creams, gels, solutions, ointments, lacquers. It is noted that the composition can also be associated with a device that contains the compositions and various supports and/or vehicles useful for delivery of the composition, for example, sticks (pins), tapes, occlusive applicators (e.g., cervical cap), and occlusive bandages. Such a device can be provided in a kit, together with the composition. The optimal percentage of the therapeutic agent in each pharmaceutical formulation varies according to the formulation itself and the therapeutic effect desired in the specific pathologies and correlated therapeutic.

[0091] As noted herein, the presently-disclosed subject matter further includes a method for the treatment of a condition affecting skin and/or a mucosal surface of a subject, which includes administering an effective amount of a composition, as described hereinabove, to the subject. In some embodiments, the composition is administered to an affected site on the skin or the mucosal surface of the subject. In some embodiments, the composition is administered topically, which can include direct administration to skin or mucosa, including intranasal, oral, and genital mucosa. In some embodiments, the composition can be injected, for example, administered by intralesional injection.

[0092] The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples. The following examples include some prophetic examples, as indicated. The following examples may include compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the present invention.

EXAMPLES

[0093] Example 1 – *In vivo* Treatment of Warts

[0094] A composition including an imidazoquinoline compound; and a retinoid agent was tested *in vivo*. Imiquimod (5% (wt/wt)) and tazarotene (0.1% (wt/wt) were combined in a 1:1 ratio. The resulting composition was topically applied to individual warts in approximately 30 patients. The patients had various types of warts (thick and thin) in varying locations including palms, soles, hands, legs, feet, trunk, and extremities (including periungual). The composition could be used occluded or non-occluded, at the patient's option.

[0095] With reference to **Figures 1** and **2**, the treatment resulted in marked improvement and resolution in many cases. This treatment was used with warts in multiple sites including the arms, legs, hands, feet, facial, and periungual areas with beneficial results. There was complete resolution in about 50% of the patients. There was about a 75%-90% reduction in size and number of warts in about 25% of the patients. There was about a 50%-75% reduction in size and number of warts in about 25% of the patients. The time for the patients to respond was about 1 week (in 5 of the patients) to about 3 months, with an average time to response of about 4-6 weeks. Some patients demonstrated a response including complete resolution without inflammation. The duration of response was shown to be prolonged in complete responders. Another noted benefit associated with the composition has been the resolution of warts at locally distant untreated sites (which may be due to increased immune recognition) as well as the decreased recurrence rate as compared to other modalities.

[0096] Patient follow-up showed no major tolerability issues. The composition was well-tolerated in the patients receiving treatment, with the most common side effect being a local minor irritation and sometimes a minor vesicular reaction (usually painless). The composition was reported to be easy to apply, convenient, and effective.

[0097] These results are in contrast to the results seen when applying imiquimod or tazarotene individually, which were not as efficacious. The composition resulted in surprisingly increased efficacy relative to the treatment with imiquimod or tazarotene individually.

[0098] Example 2 – *In vivo* Treatment of Skin Conditions (Prophetic)

[0099] A composition including an imidazoquinoline compound; and a retinoid agent is tested *in vivo*. The composition is topically applied to sites displaying a skin condition selected from a wart, *molluscum contagiosum*, a keloid, and a skin cancer, each as defined herein. The treatment results in marked improvement and resolution in many cases. The

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results are found to be more efficacious as compared to applying an imidazoquinoline compound or a retinoid agent individually.

[00100] Example 3 – *In vivo* Treatment of Skin Conditions Effecting Mucosal Surface (Prophetic)

[00101] A composition including an imidazoquinoline compound; and a retinoid agent is tested *in vivo*. The composition includes a concentration of retinoid agent (e.g., tazarotene) that is sufficiently low so as not to cause undue irritation to the mucosal surface (e.g., mouth or genitalia) of a patient. The composition is topically applied to sites displaying a skin condition selected from a wart, *molluscum contagiosum*, a keloid, and a skin cancer, each as defined herein. The treatment results in marked improvement and resolution in many cases. The results are found to be more efficacious as compared to applying an imidazoquinoline compound or a retinoid agent individually. Surprisingly, the inclusion of the retinoid agent, even at a concentration sufficiently low so as not to cause undue irritation to the mucosal surface, results in unexpected beneficial results.

[00102] Example 5 – Synergy Coefficient (Prophetic)

[00103] An animal model of hyperkeratinized skin is used to test the efficacy of an exemplary composition and the efficacy of imiquimod for treating common warts. The exemplary composition includes 5% (wt/wt) imiquimod and a 0.1% (wt/wt) tazarotene.

[00104] The comparison compound is imiquimod. Administration of the composition results in a 100% cure rate, while the treatment with imiquimod results in a 60% cure rate.

[00105] The activity ratio is calculated as follows:

$$R = AB/X_n = 100/60 = 1.67.$$

[00106] The concentration adjustment factor is calculated as follows:

$$F = 100/C_n = 100/5 = 20.$$

[00107] The synergy coefficient is therefore:

$$S = (R)(F) = (1.67)(20) = 33.34; \text{ or}$$

$$S = [(AB/X_n)(100)]/C_n = [(100/60)(100)]/5 = 33.34$$

[00108] The experiment is repeated, wherein the comparison compound is tazarotene. Administration of the composition results in a 100% cure rate, while the treatment with tazarotene results in a 40% cure rate.

[00109] According to Formula 1, the activity ratio is calculated as follows:

$$R = AB/X_n = 100/40 = 2.5$$

[00110] According to Formula 2, the concentration adjustment factor is calculated as follows:

$$F = 100/C_n = 100/0.1 = 1000$$

[00111] According to Formulae 3 and 4, the synergy coefficient is therefore:

$$S = (R)(F) = (2.5)(1000) = 2500; \text{ or}$$

$$S = [(AB/X_n)(100)]/C_n = [(100/40)(100)]/0.1 = 2500$$

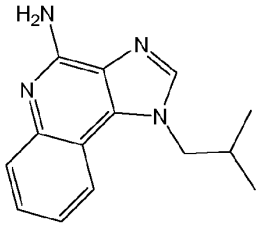
[00112] Based on the measured % effect of imiquimod (60%) and tazarotene (40%), the expected % effect of the combination is calculated according to Formula 5, as follows:

$$E = X + Y - (X*Y/100) = 60 + 40 - (60*40/100) = 76$$

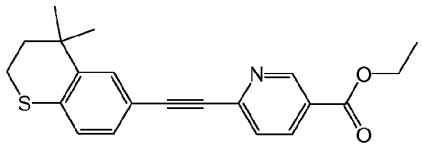
[00113] The actual % effect of the composition is 100% (A = 100). Because A = 100 > E = 76, the combination has synergy (a positive interaction of the compounds).

[00114] **Example 6 – Solubility, Compatibility, and Stability of the Composition**

[00115] The composition feasibility of a composition including both imiquimod and tazarotene was studied. Goals of the study included the following: to determine whether the imidazoquinoline compound and the retinoid agent are compatible with each other, to determine whether common solvents could be used to sufficiently dissolve the two ingredients, and to determine whether the resulting composition would be stable. The ability to produce a stable and compatible composition was uncertain at the outset of these studies, in part, given that imiquimod is well known to be a challenging molecule.



Imiquimod



Tazarotene

[00116] For this example, isostearic acid (ISA) was selected as a primary solvent, and the following additional solvents were selected based on miscibility with ISA and solubility of tazarotene: alcohol (A) (ethyl alcohol, USP (190 Proof)), benzyl alcohol (BA), diethyl sebacate (DES), mineral oil (MO), and transcutol (T).

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[00117] The compositions having solvent blends as outlined in **Table 1** were prepared to evaluate the compatibility of imiquimod (5% wt/wt) and tazarotene (0.1% wt/wt).

Table 1: Solvent Blends for to Test Compatibility of Imiquimod and Tazarotene
50:50 Isostearic Acid and Alcohol (ISA + A)
50:50 Isostearic Acid and Benzyl Alcohol (ISA + BA)
50:50 Isostearic Acid and Diethyl Sebacate (ISA + DES)
50:50 Isostearic Acid and Mineral Oil (ISA + MO)
50:50 Isostearic Acid and Transcutol (ISA + T)

[00118] Control Samples for each solution (T=0) were provided using the initial samples stored at 5°C, and analyzed after four (4) weeks. Test Samples of each solution were subjected to the following conditions: 1) storage at 25°C for four weeks; 2) storage at 40°C for four weeks; 3) storage at 50°C for four weeks; and 4) three cycles of freeze/warm (F/W) cycling (-20°C to 40°C). The physical stability of each Sample was observed and the chemical stability of imiquimod and tazarotene in each Sample was studied using chromatographic techniques.

[00119] Information regarding Physical Stability is set forth in **Table 2**.

Table 2: Physical Stability

Batch 3537-18	Description	T =0	3 cycles F/W	4 weeks 25°C	4 weeks 40°C	4 weeks 50°C
2	ISA + A	pale yellow clear solution	Conforms	Conforms	Conforms	Conforms
3	ISA + BA	pale yellow clear solution	Conforms	Conforms	Conforms	Conforms
4	ISA + DES	pale yellow clear solution	Conforms	Conforms	Conforms	Conforms
5	ISA + MO	colorless to pale yellow, clear solution	Conforms	Conforms	Conforms	Conforms
6	ISA + T	colorless to pale yellow, clear solution	Conforms	Conforms	*pale yellow solution, crystals settled at bottom	*pale yellow solution, crystals settled at bottom

Note: "Conforms" indicates appearance meets T = 0 evaluation

[00120] Information regarding Chemical Stability is set forth in **Tables 3-8**.

Table 3: Summary of Imiquimod Stability

Description	Imiquimod %Label Claim (degs, %Area)				
	T=0	3 cycles F/W	4 weeks 25°C	4 weeks 40°C	4 weeks 50°C
ISA + A	102.3	101.9	102.9	102.1	102.6 (0.08)
ISA + BA	101.3	101.3 (0.22)	101.5	102.2 (0.26)	101.5 (0.36)
ISA + DES	100.6	101.5	101.1	102.1	101.3
ISA + MO	101.4	102.4	101.4	101.7	101.8
ISA + T	102.0	101.9	101.5	Not analyzed	Not analyzed
Note: Mean values are reported					

Table 4: Summary of Tazarotene Stability

Batch 3537-18	Description	Tazarotene %Label Claim (degs, %Area)				
		T=0	3 cycles F/W	4 weeks 25°C	4 weeks 40°C	4 weeks 50°C
2	ISA + A	101.5	100.3 (0.19)	102.6	100.8 (0.18)	99.9 (0.34)
3	ISA + BA	78.6 (0.42)	66.0 (1.35)	76.2 (0.51)	63.8 (1.59)	57.8 (1.76)
4	ISA + DES	100.0	99.4	100.8	99.5	99.1
5	ISA + MO	100.9	99.9	100.5	98.4	99.1
6	ISA + T	101.6	91.4 (0.49)	100.7	Not analyzed	Not analyzed
Note: Mean values are reported						

Table 5: Tazarotene and Imiquimod Solution Stability Summary Report

Description	Condition	Imiquimod			Tazarotene		
		% LC	Degradation Products (RRT)	%Area	% LC	Degradation Products (RRT)	% Area
50:50 Isostearic Acid and Alcohol	T = 0	100.9	NC	NA	100.2	ND	NA
		103.6	ND	NA	102.8	ND	NA
	Freeze/Warm (-20 °C/40 °C	100.8	ND	NA	99.3	0.92	0.19
		103.0	ND	NA	101.3	0.92	0.19
	4 weeks at 25 °C	102.7	ND	NA	102.6	ND	NA
		103.0	ND	NA	102.5	ND	NA
	4 weeks at 40 °C	101.4	ND	NA	100.3	0.92	0.16
		102.7	ND	NA	101.2	0.92	0.19
	4 weeks at 50 °C	102.9	1.22	0.08	99.8	0.92	0.32
		102.2	1.22	0.08	100.0	0.92	0.35

Table 6: Tazarotene and Imiquimod Solution Stability Summary Report

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Description	Condition	Imiquimod			Tazarotene		
		% LC	Degradation Products (RRT)	%Area	% LC	Degradation Products (RRT)	% Area
50:50 Isostearic Acid and Benzyl Alcohol	T = 0	100.5	ND	NA	78.3	0.84	0.41
		102.0	ND	NA	78.9	0.84	0.42
	Freeze/Warm (-20 °C/40 °C	100.9	1.71	0.23	65.8	0.84 1.05	0.75 0.53 Total: 1.27
		101.7	1.71	0.21	66.2	0.84 1.05	0.94 0.48 Total: 1.42
	4 weeks at 25 °C	101.7	ND	NA	76.3	0.84	0.46
		101.3	N/D	NA	76.0	0.84	0.55
	4 weeks at 40 °C	102.4	1.71	0.26	63.7	0.84 1.05	1.03 0.59 Total: 1.62
		101.9	1.71	0.25	63.8	0.85 1.05	0.97 0.59 Total: 1.56
	4 weeks at 50 °C	101.4	1.71	0.31	57.7	0.84 1.05	1.18 0.79 Total: 1.97
		101.6	1.71	0.40	57.9	0.84 1.05	1.01 0.54 Total: 1.55

Table 7: Tazarotene and Imiquimod Solution Stability Summary Report

Description	Condition	Imiquimod			Tazarotene		
		% LC	Degradation Products (RRT)	%Area	% LC	Degradation Products (RRT)	% Area
50:50 Isostearic Acid and Diethyl Sebacate	T = 0	101.3	ND	NA	100.5	ND	NA
		99.9	ND	NA	99.5	ND	NA
	Freeze/Warm (-20 °C/40°C)	101.6	ND	NA	99.4	ND	NA
		101.3	ND	NA	99.3	ND	NA
	4 weeks at 25 °C	100.9	ND	NA	100.8	ND	NA
		101.3	ND	NA	100.8	ND	NA
	4 weeks at 40 °C	102.3	ND	NA	99.7	ND	NA
		101.8	ND	NA	99.2	ND	NA
	4 weeks at 50 °C	101.7	ND	NA	99.3	ND	NA
		100.9	ND	NA	98.8	ND	NA

Table 8: Tazarotene and Imiquimod Solution Stability Summary Report

Description	Condition	Imiquimod			Tazarotene		
		% LC	Degradation Products (RRT)	%Area	% LC	Degradation Products (RRT)	% Area
50:50 Isostearic	T = 0	100.5	ND	NA	100.3	ND	NA
		102.3	ND	NA	101.4	ND	NA
	Freeze/Warm (-20 °C/40°C)	102.9	ND	NA	100.1	ND	NA
		101.8	ND	NA	99.7	ND	NA

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Acid and Mineral Oil	4 weeks at 25 °C	101.7	ND	NA	100.4	ND	NA
		101.0	ND	NA	100.5	ND	NA
	4 weeks at 40 °C	102.1	ND	NA	98.8	ND	NA
		101.2	ND	NA	97.9	ND	NA
	4 weeks at 50 °C	101.9	ND	NA	99.3	ND	NA
		101.6	ND	NA	98.8	ND	NA

[00121] As reflected by the results presented above, the physical stability of imiquimod and tazarotene combination is shown for all Samples, with the exception of the samples including isostearic acid and transcutol (ISA +T) stored at high temperatures (40-50°C).

[00122] As also reflected by the results presented above, in all Samples analyzed, imiquimod was shown to be chemically stable, based on the fact that the mean assay values remained relatively unchanged from the initial values over 4 weeks at various temperatures.

[00123] As further reflected by the results presented above, Tazarotene is chemically stable in all the solvent blends with the exception of isostearic acid and benzyl alcohol (ISA + BA), in which it appears that BA has a negative impact on the chemical stability of tazarotene and appears to result in a temperature dependant loss of tazarotene. Tazarotene stability also appears to be impacted by exposure to F/W cycling in ISA + T.

[00124] To summarize, all analyzed Samples displayed both physical and chemical stability under certain conditions, including storage at room temperature (25°C). Furthermore, compositions of imiquimod and tazarotene in ISA plus alcohol, diethyl sebacate, or mineral oil were both physically and chemically stable under all test conditions, including storage for four weeks at 5°C, 25°C, 40°C, and 50°C, as well as conditions including three rounds of freeze/ warm cycling.

[00125] **Example 7 – *In Vitro* Percutaneous Absorption Studies using Human Tissue**

[00126] To characterize the effect of providing a composition including both an imidazoquinoline compound and a retinoid agent on the penetration of the composition as compared to an imidazoquinoline compound alone, absorption studies were conducted using human tissue. For the study described in this example, varying concentrations of tazarotene were evaluated while keeping the concentration of imiquimod constant (5%w/w).

[00127] Data from this *in vitro* skin permeation study indicate a trend in the efficiency of delivery of Imiquimod. Imiquimod delivery, expressed as a sum of all the delivery values for each of the three evaluated compartments, has a consistent response to the addition of Tazarotene: Delivery of Imiquimod increases with the addition of Tazarotene.

[00128] DMSO based controls are used because they usually yield higher delivery of actives through the skin. In this case, the DMSO control (which included Tazarotene) did not give a higher degree of penetration, indicating that imiquimod delivery is independent of the choice of solvent, but instead is due to the addition of tazarotene.

[00129] **Methods**

[00130] This *in vitro* percutaneous absorption study was conducted using procedures adapted from the FDA and AAPS Report of the Workshop on Principles and Practices of *In Vitro* Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence (Skelly et al., 1987). All evaluated compositions were prepared by DPSI. The compositions of all the compositions evaluated in this study are summarized in **Table 9**.

Table 9: Test Samples

Sample ID*	Description	% (w/w) Tazarotene	% (w/w) Imiquimod
3537-25-1	Tazarotene (T)	0.10	0.00
3537-25-2	Imiquimod (I)	0.00	5.00
3537-25-3	1:500	0.01	5.00
3537-25-4	1:100	0.05	5.00
3537-25-5	1:50	0.10	5.00
3537-26-1	1:10	0.50	5.00
3537-26-2	1:5	1.00	5.00
3537-26-3 3537-28-3**	DMSO Control – 1:50	0.10	5.00

* All samples were provided in 50:50 Isostearic Acid and Alcohol (ISA + A), except the DMSO Control, which was provided in 80:20 DMSO and Isostearic Acid.

** Sample IDs 3537-28-3 is identical to 3537-26-3.

Sample IDs 3537-28-3 and 3537-25-1 were used as positive and negative controls for Imiquimod permeation, respectively.

[00131] The clinically relevant dose of 5 mg/cm^2 was applied to dermatomed human abdominal tissue from a single donor obtained following elective surgery. The thickness of the tissue ranged from 0.023 – 0.032 inches (0.584 – 0.813 mm) with a mean +/- standard

deviation in thickness of 0.027 +/- 0.003 inches (0.677 +/- 0.066 mm) and a coefficient of variation of 10%.

[00132] Percutaneous absorption was evaluated using this human abdominal tissue from a single donor mounted in Bronaugh flow-through diffusion cells. The cells were maintained at a constant temperature of 32°C by use of recirculating water baths. These cells have a nominal diffusion area of 0.64 cm^2. Fresh receptor phase (PBS, pH 7.4, containing 0.1% sodium azide and 4% Bovine Serum Albumin) was continuously pumped under the tissue at a flow rate of nominally 0.25 ml/hr and collected in 6-hour intervals. The receptor phase samples were collected in pre-weighed scintillation vials; the post weights were taken at the end of the study. Following the 24-hour duration exposure, the composition residing on the tissue surface was removed by tape-stripping with CuDerm D-Squame stripping discs. The epidermis, dermis, and receptor phase samples were labeled and frozen prior to subsequent analysis of Tazarotene and Imiquimod content by LC/MS/MS and ultimate sample disposal.

[00133] Tissue permeation and deposition results were statistically evaluated using unpaired student's t-tests (significant differences between compositions were defined by a *p*-value of < 0.05, at the 95% confidence interval).

[00134] **Results**

[00135] Epidermis, Dermis, and Receptor.

[00136] With reference to **Table 10**, Column 5, data showing cumulative penetration of imiquimod based on a 5 mg/cm^2 dose is presented as percent of applied dose (Sub-column A) and calculated ng/cm^2 following a theroretical dose of 5 mg composition/cm^2.

[00137] With regard to efficiency of delivery, the total amount of imiquimod present ranged from 1.93 to 4.07 percent of the applied dose of Imiquimod. Compositions 3537-25-4 and 3537-26-1 had the highest efficiency of delivery with 3.07 and 4.07 perecent of the applied dose of Imiquimod, respectively. Composition 3537-25-2, the only composition that did not contain tazarotene, exhibited the least efficient delivery with 1.93 percent of the applied dose.

[00138] With regard to total amount of Imiquimod delivered, the calculated amount ranged from 4833 to 10186 ng/cm^2. Compositions 3537-25-4 and 3537-26-1 had the highest total Imiquimod with 7682 and 10186 ng/cm^2, respectively. Composition3537-25-2, the only composition that did not contain tazarotene, generated the lowest total levels of Imiquimod,

with 4833 ng/cm^2. The data presented in Table 10, Column 5, Sub-column B are presented graphically in Figure 2.

Table 10: Cumulative Receptor Phase and Tissue Levels of Imiquimod Following 24 Hours of Topical Exposure

Formulation ID		Receptor Content at 24 Hours		Epidermis		Dermis		Dermis + Receptor Mean		Epidermis +Dermis + Receptor Mean	
		% Dose Applied	Calculated ng/cm2 Api for Formulation Dose of 5 mg/cm2	% Dose Applied	Calculated ng/cm2 Api for Formulation Dose of 5 mg/cm2	% Dose Applied	Calculated ng/cm2 Api for Formulation Dose of 5 mg/cm2	% Dose Applied	Calculated ng/cm2 Api for Formulation Dose of 5 mg/cm2	% Dose Applied	Calculated ng/cm2 Api for Formulation Dose of 5 mg/cm2
A)	Mean	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ID:3537-25-1	SD	0.00	0.00	0.00	0.00	0.00	0.00				
	%CV	N/A	N/A	N/A	N/A	N/A	N/A				
B)	Mean	0.018	46.2	1.80	4492	0.118	295	0.136	341		4833
ID:3537-25-2	SD	0.008	20.5	0.52	1292	0.028	71				
	%CV	44	44	29	29	24	24				
C)	Mean	0.018	44.2	2.40	5991	0.186	466	0.204	510		6501
ID:3537-25-3	SD	0.006	16.0	0.39	985	0.097	243				
	%CV	36	36	16	16	52	52				
D)	Mean	0.016	39.1	2.79	6971	0.269	672	0.284	711		7682
ID:3537-25-4	SD	0.005	13.3	1.00	2489	0.217	543				
	%CV	34	34	36	36	81	81				
E)	Mean	0.015	37.2	2.53	6331	0.193	483	0.208	520		6851
ID:3537-25-5	SD	0.005	12.5	0.79	1982	0.102	255				
	%CV	34	34	31	31	53	53				
F)	Mean	0.016	40.3	3.76	9405	0.296	741	0.312	781		10186
ID:3537-26-1	SD	0.005	11.9	1.33	3336	0.164	410				
	%CV	29	29	35	35	55	55				
G)	Mean	0.024	60.1	1.93	4830	0.186	466	0.211	526		5356
ID:3537-26-2	SD	0.028	70.8	0.55	1380	0.080	200				
	%CV	118	118	29	29	43	43				
H)	Mean	0.026	63.9	2.27	5667	0.268	670	0.294	734		6401
ID:3537-28-3	SD	0.005	11.5	0.58	1449	0.105	263				
	%CV	18	18	26	26	39	39				

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[00139] Efficiency of Delivery

[00140] Tissue permeation and deposition of Imiquimod are summarized in **Table 10** and presented in units of percent of applied dose and calculated ng/cm^2 following a theoretical dose of 5 mg composition/cm^2.

[00141] *Tissue permeation (receptor phase levels).* With reference to **Table 10**, Column 1, Sub-Column A, tissue permeation (receptor phase levels) after 24 hours ranged from 0.015 to 0.026 percent of the applied dose of Imiquimod.

[00142] *Dermal deposition.* With reference to **Table 10**, Column 3, Sub-Column A, dermal deposition of Imiquimod from the evaluated compositions ranged from 0.118 to 0.296 percent of the applied dose. Composition 3537-25-4 and 3537-26-1 had the highest efficiency of Imiquimod dermal deposition with 0.269 and 0.296 percent of the applied dose respectively. The lowest efficiency of Imiquimod dermal deposition was produced by Composition 3537-25-2 with 0.118 % percent of the applied dose.

[00143] *Epidermal deposition.* With reference to **Table 10**, Column 2, Sub-Column A, epidermal deposition of Imiquimod from the evaluated compositions ranged from 1.80 to 3.76 percent of the applied dose. Compositions 3537-25-4 and 3537-26-1 had the highest efficiency of Imiquimod epidermal deposition with 2.79 and 3.76 percent of the applied dose, respectively. The lowest efficiency of Imiquimod epidermal deposition was generated by Composition 3537-25-2.

[00144] Total Amount Delivered

[00145] *Tissue permeation (receptor phase levels).* With reference to **Table 10**, Column 1, Sub-Column B, the total amount of Imiquimod delivered from a composition is dependent upon the concentration of Imiquimod in the product as well as the efficiency of delivery (percent of applied dose). Calculated mass of Imiquimod permeating the tissue following a dose of 5 mg composition per square centimeter of skin for 24 hours (receptor phase levels) ranged from 37.2 to 60.1 ng/cm^2 of Imiquimod. Compositions 3537-25-2 and 3537-26-2 had the highest delivery of Imiquimod with 46.2 and 60.1 ng/cm^2, respectively, whereas the lowest efficiency of Imiquimod delivery was with 3537-25-5. A kinetic profile of tissue permeation is presented in **Figure 3**, where the cumulative tissue permeation of Imiquimod in units of ng/cm^2 is plotted against time in hours.

[00146] *Dermal deposition.* With reference to **Table 10**, Column 3, Sub-Column B, the calculated Imiquimod dermal deposition ranged from 295 to 741 ng/cm^2. Compositions

3537-25-4 and 3537-26-1 had the highest Imiquimod dermal deposition with 672 and 741 ng/cm^2, respectively. Composition 3537-25-2 Composition produced the lowest Imiquimod dermal deposition, 295 ng/cm^2. These results are presented graphically in **Figure 4**, which shows dermal levels of Imiquimod following 24 hour duration of topical exposure in unit(s) of ng/cm^2.

[00147] *Epidermal deposition.* With reference to **Table 10**, Column 2, Sub-Column B, the calculated Imiquimod epidermal deposition ranged from 4,492 to 9,405 ng/cm^2. Compositions 3537-25-4 and 3537-26-1 had the highest Imiquimod epidermal deposition with 6,971 and 9,405 ng/cm^2, respectively. Composition 3537-25-2 generated the lowest Imiquimod epidermal deposition, 4,492 ng/cm^2. These results are presented graphically in **Figure 5**, which shows epidermal levels of Imiquimod following 24 hour duration of topical exposure in unit(s) of ng/cm^2.

[00148] *Dermis and Receptor* (combined values). With reference to **Table 10**, Column 4, Sub-Column B, the total amount of Imiquimod present in the dermal and receptor compartments was assessed by calculating the total calculated mass/cm^2 [ng/cm^2] for a composition dose of 5mg/cm^2 present in the dermis (D) and receptor (R) compartments. Subsequently, the mean values of six replicates were determined and defined as D+R. The calculated mean D+R values provided an indication of the total amount of API that penetrated the epidermis. Mean D+R ranged from 341 to 781 ng/cm^2 of Imiquimod. Compositions 3537-25-4 and 3537-26-1 yielded the highest D+R values, respectively. The lowest D+R was associated with Composition 3537-25-2. These results are presented graphically in **Figure 6**, which shows D+R levels of Imiquimod following 24 hour duration of topical exposure in unit(s) of ng/cm^2.

[00149] **Conclusions**

[00150] Data from this study demonstrate a trend in the efficiency of delivery of Imiquimod. Imiquimod delivery, expressed as a sum of all the delivery values for each of the three evaluated compartments, has a consistent response to the addition of Tazarotene: Delivery of Imiquimod increases with the addition of Tazarotene.

[00151] With reference to **Figure 2**, showing the cumulative penetration of Imiquimod, the data consistently show that any addition of tazarotene to the composition will improve the penetration of imiquimod, surprisingly, even at concentrations as much as 10 times lower (0.01% (w/w)) than the concentration at which tazarotene is currently in clinical use (0.1% (w/w)). Unexpectedly, compositions including doses of tazarotene as low as 0.01% appear to provide for similar levels of penetration as compared to compositions

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including a 0.1% concentration of tazarotene. Also, surprisingly, it appears that concentrations of tazarotene that are higher (1%) or relatively higher as compared to imiquimod (1:5 ratio) were less effective than lower concentrations.

[00152] Another unexpected finding was associated with the positive control (3537-28-3), which contained DMSO, but apart from the solvent was identical to composition 3537-25-5. DMSO based controls are used because they usually yield higher delivery of actives through the skin. In this case, the DMSO control (which included Tazarotene) did not give a higher degree of penetration, indicating that imiquimod delivery is independent of the choice of solvent, but instead is due to the addition of tazarotene. Indeed, as compared to the sample including Imiquimod without tazarotene (3537-25-2), all test samples including any concentration of tazarotene were found to improve penetration of Imiquimod.

[00153] As contemplated by the present inventor, composition including imiquimod and tazarotene have increased penetration, as compared to imiquimod individually. It is believed that the increased penetration can be correlated to an increased effectiveness of imiquimod. Without wishing to be bound by theory or mechanism, the increased penetration is believed to result from an ability of tazarotene to decrease the thickness of a layer of keratin in the virally infected cells. Tazarotene also decreases keratinocyte proliferation and increases the maturation phase of the virally infected cells thus thinning the thick skin that often covers warts. The combination also allows for a dilution of the tazarotene and its potential for local irritancy. Indeed, with the surprising efficacy at lower concentrations of tazarotene, certain embodiments of the composition can be readily prepared to limit irritancy and/or for areas prone to irritation. The compositions of the presently-disclosed subject matter will allow for increased tolerance, efficacy, compliance, and ease of use. When the imiquimod and tazarotene are used separately, the effects of both are diminished, and if applied at different points in time there is a decrease in compliance as well as the loss of the beneficial effect noted when utilized simultaneously in compositions of the presently-disclosed subject matter.

[00154] As noted herein, synergistic clinical results are achieved by combining an imidazoquinoline compound and a retinoid agent in a single composition. Without wishing to be bound by theory or mechanism, in addition to benefits achieved due to increased penetration of the imidazoquinoline compound, as facilitated by the retinoid agent, each component of the composition has an active role in treating the condition of interest, and each improves the effect of the other by virtue of being provided in a single composition for administration. For example, in addition to increasing the penetration of the

imidazoquinoline compound, the retinoid agent has an effect in treating the condition of interest, and such effect is improved in the presence of the imidazoquinoline compound. Similarly, in addition to having increased penetration in the presence of the retinoid agent, the imidazoquinoline compound has an improved effect in treating the condition of interest in the presence of the retinoid agent. In this regard, the combination of the imidazoquinoline compound and the retinoid agent can achieve synergistic results in the treatment of a condition affecting skin and/or a mucosal surface of a subject, which are in addition to mere additive effect. In some embodiments, the synergistic results are in addition to effects resulting from increased penetration of the imidazoquinoline compound in the presence of the retinoid agent. As is further contemplated, and without wishing to be bound by theory or mechanism, it believed that biochemical chemical pathways related to conditions of interest are impacted in a synergistic manner in the presence of both the imidazoquinoline compound and the retinoid agent (e.g., imiquimod and tazarotene), such that the imidazoquinoline compound has improved efficacy in the presence of the retinoid agent and, similarly, the retinoid agent has improved efficacy in the presence of the imidazoquinoline compound.

INCORPORATION BY REFERENCE

[00155] All publications, patents, and patent applications mentioned in this specification, including those set forth in the following list, are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

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CLAIMS

What is claimed is :

1. A composition, comprising:
an imidazoquinoline compound; and
a retinoid agent.

2. The composition of claim 1, wherein the imidazoquinoline compound is selected from the group consisting of: imiquimod, resiquimod, and sotirimod.

3. The composition of claim 1, wherein the imidazoquinoline compound is imiquimod.

4. The composition of claim 1, wherein the imidazoquinoline compound is resiquimod.

5. The composition of claim 1, wherein the imidazoquinoline compound is sotirimod.

6. The composition of any one of the prior claims, wherein the retinoid agent is selected from the group consisting of: retinol, retinal, retinyl acetate, retinaldehyde, retinyl palmitate, retinoic acid, retinyl propionate, retinyl linoleate, dehydroretinol, eretinate, eretrin, motretinide, tazarotene, isotretinoin, tretinoin, adapalene, bexarotene, fenretinide, and alitretinoin.

7. The composition of claim any one of the prior claims, wherein the retinoid agent is tazarotene.

8. The composition of claim 1, wherein the imidazoquinoline compound is imiquimod and the retinoid agent is tazarotene.

9. The composition of any one of the prior claims, and further comprising one or more ingredient selected from the group consisting of: salicylic acid, urea, an alpha hydroxyl

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acid, and a beta hydroxyl acid.

10. The composition of any one of the prior claims, wherein the composition is provided for the treatment of a condition affecting the skin and/or mucosal surfaces of a subject.

11. The composition of claim 10, wherein the condition is selected from a wart, *molluscum contagiosum*, a keloid, and a skin cancer.

12. The composition of claim 10, wherein the condition is a wart.

13. The composition of claim 12, wherein the wart is caused by a papillomavirus.

14. The composition of claim 12, wherein the wart is caused by a human papollomaviruses (HPV).

15. The composition of claim 12, wherein the wart is selected from: *verruca vulgaris* (common wart), *verruca plana* (flat wart) *condyloma acuminatum* or *verruca acuminate* (genital wart), and *verruca pedis* (plantar wart).

16. The composition of claim 10, wherein the condition is *Molluscum contagiosum*.

17. The composition of claim 10, wherein the condition is a keloid scar.

18. The composition of claim 10, wherein the condition is a hypertrophic scar.

19. The composition of claim 10, wherein the condition is a skin cancer.

20. The composition of claim 19, wherein the skin cancer is a premalignant skin cancer.

21. The composition of claim 19, wherein the skin cancer is a malignant skin

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cancer.

22. The composition of claim 19, wherein the skin cancer is selected from melanoma and non-melanoma skin cancers, actinic keratoses, basal cell carcinomas, squamous cell carcinoma-in-situ or Bowen's disease, melanoma in-situ, and other unresectable carcinomas.

23. The composition of claim 19, wherein the skin cancer is actinic keratoses.

24. The composition of claim 19, wherein the skin cancer is a primary skin cancer.

25. The composition of claim 19, wherein the skin cancer is a secondary skin cancer.

26. The composition of claim 19, wherein the skin cancer is selected from : cutaneous T-cell lymphoma, extramammary Paget's disease, lentigo maligna, cutaneous melanoma metastases, and cutaneous leishmaniasis.

27. The composition of claim 10, wherein the condition is affecting a mucosal surface of the subject

28. The composition of claim 10, wherein the subject is a human.

29. The composition of claim 10, wherein the subject is a transplant patient.

30. The composition of claim 10, wherein the subject is receiving antirejection therapy following a transplant.

31. The composition of any one of the prior claims, wherein the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt).

32. The composition of any one of the prior claims, wherein the retinoid agent is

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provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt).

33. The composition of any one of the prior claims, wherein the retinoid agent is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.025% (wt/wt).

34. The composition of any one of the prior claims, wherein the retinoid agent is provided in the composition at a final concentration between about 0.5% (wt/wt) and about 0.01% (wt/wt).

35. The composition of any one of the prior claims, wherein the retinoid agent is tazarotene provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt).

36. The composition of claim 35, wherein the tazarotene is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt). I

37. The composition of claim 35, wherein the tazarotene is provided in the composition at a final concentration between about 1% (wt/wt) and about 0.025% (wt/wt).

38. The composition of claim 35, wherein the tazarotene is provided in the composition at a final concentration between about 0.5% (wt/wt) and about 0.01% (wt/wt).

39. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 1% (wt/wt).

40. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.5% (wt/wt).

41. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.1% (wt/wt).

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42. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.05% (wt/wt).

43. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.01% (wt/wt).

44. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.005% (wt/wt).

45. The composition of claim 35, wherein the tazarotene is provided at a concentration of about 0.001% (wt/wt).

46. The composition of any one of the prior claims, wherein the imidazoquinoline compound is provided in the composition at a final concentration between about 10% (wt/wt) and about 0.1% (wt/wt).

47. The composition of any one of the prior claims, wherein the imidazoquinoline compound is provided in the composition at a final concentration between about 7% (wt/wt) and about 3% (wt/wt).

48. The composition of any one of the prior claims, wherein the imidazoquinoline compound is imiquimod provided in the composition at a final concentration between about 10% (wt/wt) and about 0.1% (wt/wt).

49. The composition of claim 48, wherein the imiquimod is provided in the composition at a final concentration between about 7% (wt/wt) and about 3% (wt/wt).

50. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 10% (wt/wt).

51. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 5% (wt/wt).

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52. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 3.75% (wt/wt).

53. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 1% (wt/wt).

54. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 0.5% (wt/wt).

55. The composition of claim 48, wherein the imiquimod is provided at a concentration of about 0.1% (wt/wt).

56. The composition of any one of the prior claims, wherein composition allows for increased penetration of the imidazoquinoline compound.

57. The composition of any one of the prior claims, wherein the composition including a combination of the imidazoquinoline compound and the retinoid agent has a synergistic effect.

58. The composition of any one of the prior claims, wherein the imidazoquinoline compound and the retinoid agent are provided in formulation that includes a solvent.

59. The composition of claim 58, wherein the solvent includes isostearic acid.

60. The composition of claim 59, wherein the solvent further includes alcohol, diethyl sebacate, or mineral oil.

61. The composition of any one of the prior claims, wherein the composition is substantially stable at a temperature of 50°C for a period of four (4) weeks.

62. The composition of any one of the prior claims, wherein the composition is substantially stable at a temperature of 40°C for a period of four (4) weeks.

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63. The composition of any one of the prior claims, wherein the composition is substantially stable at a temperature of 25°C for a period of four (4) weeks.

64. The composition of any one of the prior claims, wherein the composition is substantially stable following up to three freeze/warm cycles from -20°C to 40°C.

65. The composition of claim 1, wherein the composition is formulated for topical delivery.

66. The composition of claim 1, wherein the imidazoquinoline compound is imiquimod provided in the composition at a final concentration between about 10% (wt/wt) and about 0.1% (wt/wt); the retinoid agent is tazarotene provided in the composition at a final concentration between about 1% (wt/wt) and about 0.001% (wt/wt); and the composition is substantially stable at a temperature of 25°C for a period of four (4) weeks.

67. The composition of claim 66, wherein the composition is substantially stable at a temperature of 50°C for a period of four (4) weeks.

68. A pharmaceutical composition of any one of the prior claims.

73. A kit, comprising: a composition of any one of the prior claims, and a device useful for administration of the composition.

74. The kit of claim 73, wherein the device is selected from the group consisting of: a stick, tape, an occlusive applicator, and an occlusive bandage.

75. A method for the treatment of a condition affecting skin and/or a mucosal surface of a subject, comprising: administering an effective amount of a composition of any one of the prior claims.

76. The method of claim 75, wherein the composition is administered to an affected site on the skin and/or mucosal surface of the subject.

77. The method of claim 75, wherein the composition is administered topically.

78. The method of claim 75, wherein the composition is administered by intralegional injection

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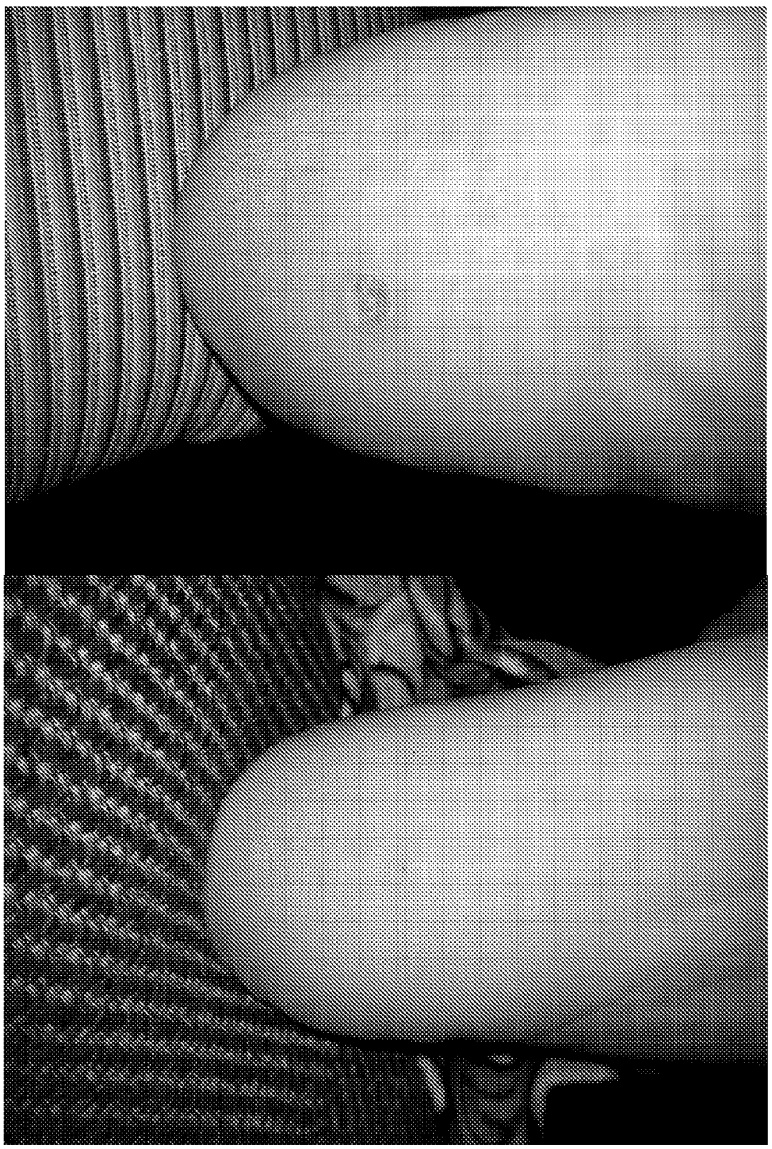


FIGURE 1A

FIGURE 1B

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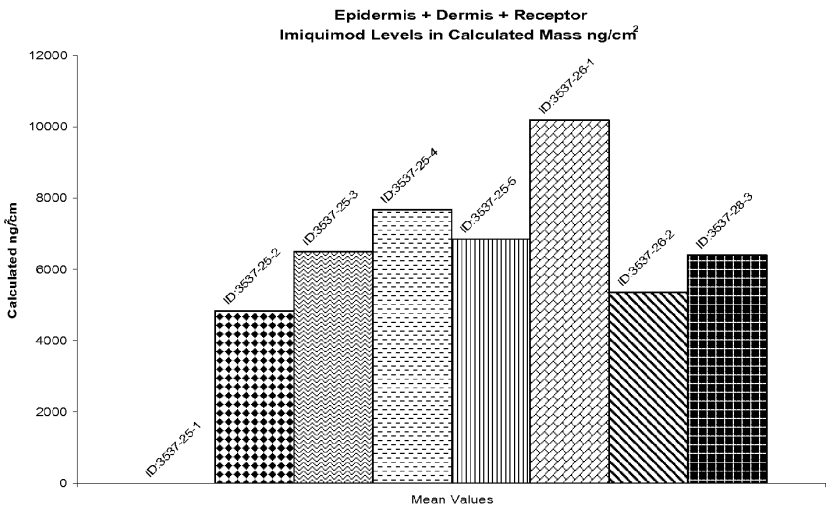

Epidermis + Dermis + Receptor
Imiquimod Levels in Calculated Mass ng/cm²
Calculated ng/cm
12000
10000
8000
6000
4000
2000
0
ID:3637-25-1
ID:3637-26-2
ID:3637-25-3
ID:3637-25-4
ID:3637-25-5
ID:3637-26-1
ID:3637-26-2
ID:3637-28-3
Mean Values

FIGURE 2

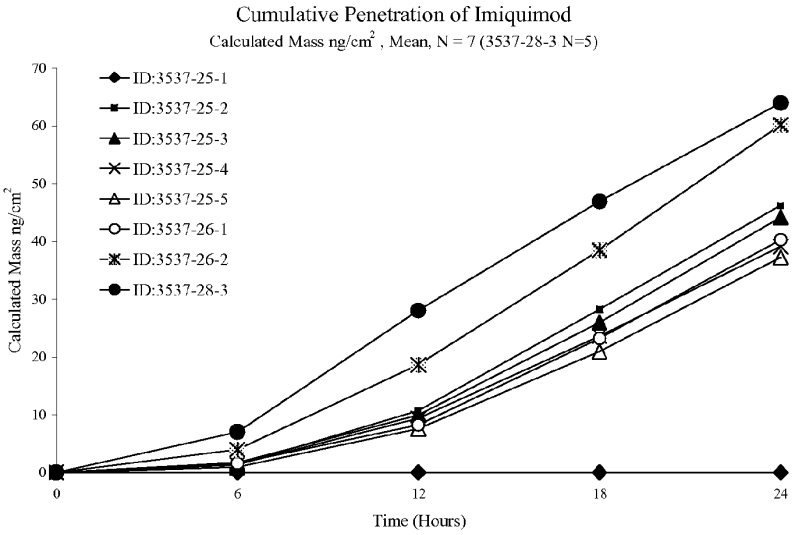


FIGURE 3

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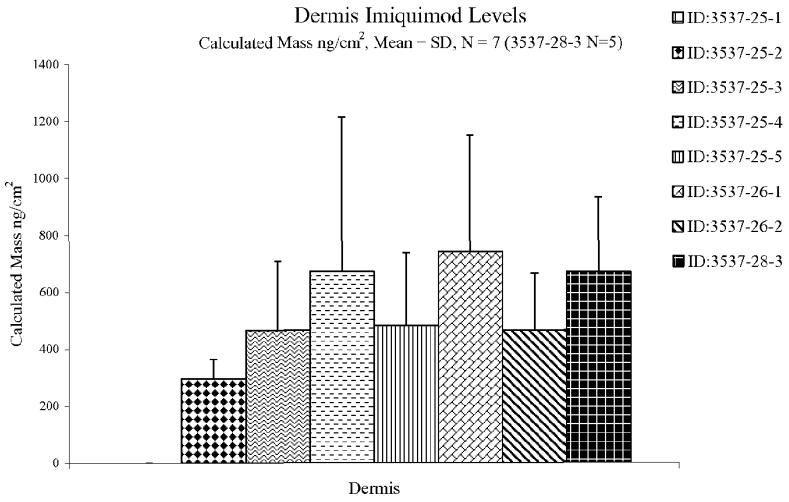


FIGURE 4

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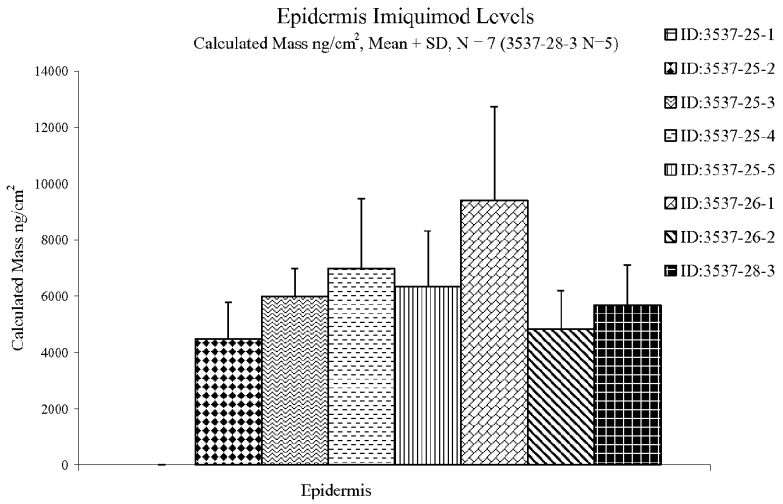


FIGURE 5

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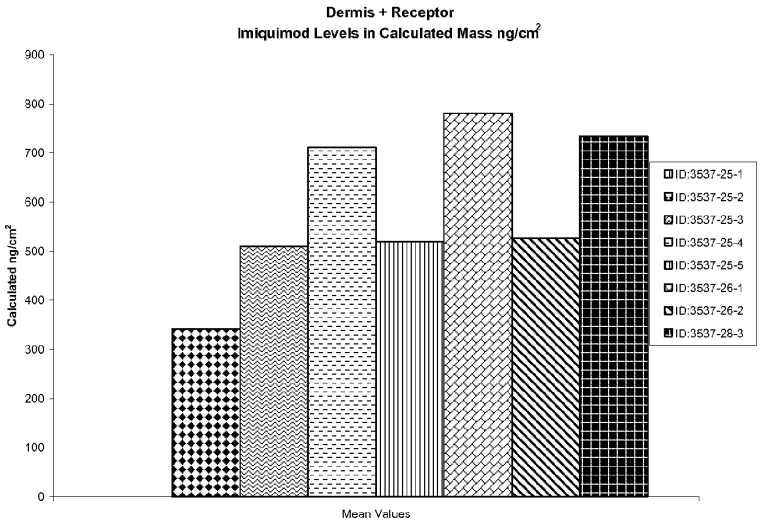

Dermis + Receptor
Imiquimod Levels in Calculated Mass ng/cm2
Calculated ng/cm2
900
800
700
600
500
400
300
200
100
0
Mean Values
ID:3537-25-1
ID:3537-25-2
ID:3537-25-3
ID:3537-25-4
ID:3537-25-5
ID:3537-26-1
ID:3537-26-2
ID:3537-26-3

FIGURE 6

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(54) Title: SHORT CONTACT TREATMENT OF PSORIASIS WITH TOPICAL RETINOIDS

(57) Abstract

The present invention relates to a method of treating psoriasis using short–term contact with a topically–applied retinoid composition.

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SHORT CONTACT TREATMENT OF PSORIASIS WITH TOPICAL RETINOIDS

BACKGROUND OF THE INVENTION

The present invention is directed to the treatment of psoriasis using topical retinoids.

The retinoids are a family of compounds including vitamin A, retinoic acid (RA), related derivatives of these, and other compounds capable of binding to retinoic acid receptors (RAR). RA, which is a natural metabolite of vitamin A (retinol), is known as a potent modulator (i.e., an inhibitor or, to the contrary, a stimulator, depending on the nature of the cells treated) of the differentiation and proliferation of many normal or transformed cell types. All-*trans*-RA (tretinoin) acts on the differentiation and proliferation of cells by interacting with RARs contained in the cell nucleus. There are, to date, three identified subtypes of known RAR receptors, respectively termed RAR-α, -β, -γ. These receptors, after binding the RA ligand, interact with the promoter region of genes regulated by RA at specific response elements. To bind to the response elements, the RARs heterodimerize with another type of receptor designated as RXR. The natural ligand of RXRs is 9-*cis*-retinoic acid.

Many retinoids are known and have been described to date. Generally, retinoids can be identified by their ability to bind RARs, either as all the RARs or selectively to an individual RAR class. Further, retinoids exhibit a diverse spectrum of activities. Among these is use as a topical therapeutic for treatment of skin conditions.

There is presently in use an FDA approved treatment for psoriasis employing tazarotene topical gel that is marketed by Allergan, Inc. under the brand name Tazorac™. Moreover, tretinoin, also known by the tradename Retin-A™, and adapalene are approved for topical use to treat skin conditions.

The mechanism of action in the treatment of psoriasis with tazarotene or other retinoids is not known. The current FDA-approved therapeutic regimen requires Tazorac™ gel to be applied topically in its 0.05% or its 0.1% formulation and

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left on the affected skin for long periods of time, e.g. overnight. It is generally applied in the evening and left in place until routine washing in the morning. Thus, in the treatment of psoriasis, the Tazorac™ gel would typically be left on the skin for 8 to 12 hours.

Unfortunately, a major shortcoming of this course of treatment is that adverse skin reactions are experienced by a significant portion of users. These reactions include pruritus, burning/stinging and erythema (sometimes severe), actual worsening of psoriasis, irritation and skin pain. Since the treatment regimen is usually prolonged, covering many weeks or months, any adverse reactions are rendered even more substantial in the perception of the user, often resulting in the interruption or abandonment of the treatment regimen. Thus the adverse reactions are not merely significant in-and-of themselves, but can make treatment ineffectual due to the inability or unwillingness of the user to follow the regimen.

To overcome these shortcomings, it has now been found that topically-applied retinoids can be used to treat psoriasis using a short-contact treatment regimen. For example, tazarotene has been used for short-contact therapy to treat psoriasis as disclosed in co-pending application entitled "Short Contact Treatment of Psoriasis with Tazarotene Compositions," filed on the same day as this application by the same inventors and which is hereby incorporated herein by reference.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating psoriasis in a human patient by topically applying an effective amount of a retinoid composition to the affected area of a patient's skin, allowing that composition to remain in contact with the skin for a period of from about thirty seconds to about thirty minutes, followed by rinsing the composition from the affected area. Generally, the short contact treatment is performed once a day at least three times a week as long as treatment is needed. In preferred embodiments, the active retinoid in the composition is tazarotene, tretinoin or adapalene and, more preferably, is tazarotene.

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DESCRIPTION OF THE INVENTION

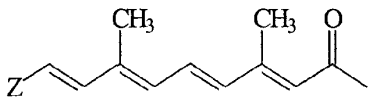
According to the invention, it has been found that short-contact retinoid therapy yields surprisingly improved and beneficial results in the treatment of psoriasis.

"Short-contact retinoid therapy", as used herein, is intended to distinguish over conventional, or extended-contact, treatment(s) the retinoid of interest is applied to a patient's skin (typically once a day) and left on the skin indefinitely or until routine washing or showering occurs after a prolonged period of time (typically overnight).

In accordance with the invention, short-contact retinoid therapy thus comprises the steps of applying a retinoid composition to an affected area of the skin for a brief time period followed by rinsing of the skin / affected area. For psoriasis, the usual contact time is from about 30 seconds to about 30 minutes, preferably for a period of from about 5 to about 10 minutes. Immediately following the prescribed period of time, the skin is rinsed thoroughly, typically with lukewarm water.

For psoriasis therapy, the short-contact treatments are generally applied to the affected area(s) once or twice a day, preferably once a day, and repeated at least three times a week. If desired or needed, the treatments can be repeated daily. The overall duration of therapy is continued for as long as the conditions exist, i.e., until the plaques are gone or have disappeared, and can readily be determined by the patient's doctor.

In accordance with the invention and as used herein, a "retinoid composition" comprises therapeutically-active retinoids, or pharmaceutically-acceptable salts thereof, in admixture with a pharmaceutically acceptable carrier. The therapeutically-active retinoids of the invention are selected from the group consisting of a retinoic acid; retinol; therapeutically-active retinoic acid derivatives; therapeutically-active carboxylic acids represented by the formula



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and retinoids which are C20 or C22 desmethyl vinylogs of said groups, wherein Z is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group or a cyclohexenyl group, and said phenyl or naphthyl group can be substituted with from 0 to 5 substitutents selected from the group consisting of halo, hydroxy, alkyl, alkyoxy, amino, cyano or carbalkoxy, and wherein double bonds in the polyene chain of any of said groups can have a *cis* or *trans* configuration; acetylenic retinoids; adapalene; adapalene derivatives and any compound, natural or synthetic, which possesses the topical biological activity of retinoic acid in the skin and/or the ability to bind to one or more RARs; as well as the geometric isomers and sterioisomers of any of these compounds.

Examples of retinoids contemplated by the invention can be found in U.S. Patent Nos. 4,476,056; 4,105,681; 4,215,215; 4,054,589 and 3,882,244. Retinoids include both *cis* and *trans* forms having therapeutic activity. The retinoids can include a 9-*cis* double bond, a 13-*cis* double bond or a 13-*trans* double bond. Derivatives of retinoic acid include, but are not limited to, esters, amides, other biologically active forms of retinoic acid such as those with a chemical modification or substitution of a substituent of the molecule, and the like. Derivatives of adapalene include, but are not limited to, esters and amides of the naphthoic acid moiety, other biologically active forms of adapalene such as those having a chemical modification or substitution on some part of the molecule while retaining activity, and the like.

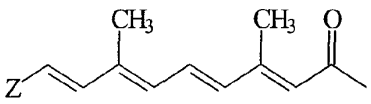
A pharmaceutically acceptable salt may be prepared for any compound of this invention having a functionality capable of forming such salt, for example an acid or amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

The preferred compounds of the invention include, but are not limited to, retinoic acid including tretinoin, 13-*cis* retinoic acid, 9-*cis*-retinoic acid, acetylenic retinoids including tazarotene and adapalene.

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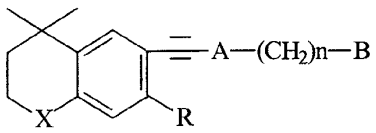
As used herein a "therapeutically-active retinoid" is a compound which, when applied topically, exhibits or possesses a biological action similar to retinoic acid (i.e., similar to vitamin A acid). Hence, these retinoids include those compounds, synthetic or natural, which have one or more of the therapeutic activities known for retinoic acid. Such activities include but are not limited to binding to and activating RARs, treating and preventing cancer and other proliferative disorders, acting as differentiating agents or anti-proliferatives agents and anti-tumor activity.

As used herein "vinylogs" are desmethyl retinoyl groups having 1 or 2 additional vinyl groups relative to retinoic acid. For example such compounds include 2,6,6,-trimethyl-1-(10'-carboxy-deca-1',3',5',7',9'-pentaenyl)cyclohex-1-ene and 2,6,6-trimethyl-1-(12'-carboxy-dodeca-1',3',5',7',9',11'-hexaenyl)cyclohex-1-ene. These groups are also referred to as C20 and C22 vinylogs of desmethyl retinoic acid and are described in U.S. Patent No. 3,882,244. The vinylogs of this invention can be prepared from a retinoyl group, any therapeutically active retinoid carboxyl group, or any group of the formula



wherein Z is as defined herein.

The acetylenic retinoids of the invention are the compounds of the formula represented by



wherein X is S, O, or NR′ where R′ is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-2; and B is H, —COOH or a pharmaceutically acceptable salt, ester or amide thereof,

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—CH_2OH or an ether or ester derivative, or —CHO or an acetal derivative, or —COR_1 or a ketal derivative where R_1 is —$(CH_2)_mCH_3$ where m is 0-4.

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where A is —COOH, this term covers the products derived from treatment of this function with alcohols. Where the ester is derived from compounds where A is —CH_2OH, this term covers compounds of the formula —CH_2OOCR where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Here, and where ever else used, lower alkyl means having 1-6 carbon atoms. Also preferred are the phenyl or lower alkylphenyl esters.

The term "amide" has the meaning generally accorded that term in organic chemistry. In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl amines. Also preferred are mono- and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals includes the radicals of the formula —CK where K is $(—OR)_2$. Here, R is lower alkyl. Also, K may be —OR_1O— where R_1 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

The preferred acetylenic retinoid compounds of this invention are those where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions in the nicotinic acid nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or the 5 and 2 positions respectively of a thiophene group respectively; n is 0; and B is

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—COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester, or —CH_2OH and the lower alkyl esters and ethers thereof, or —CHO and acetal derivatives thereof.

The preferred compounds include:

ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-nicotinate;

6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid;

ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinate;

ethyl 6-(2-(4,4,7-trimethylthiochroman-6-yl)ethynyl)-nicotinate;

ethyl 6-(2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl)nicotinate;

ethyl 5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)thiophene-2-carboxylate;

6-(2-4,4-dimethylthiochroman-6-yl)-ethynyl)-3-pyridylmethanol; and

2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-5-pyridinecarboxaldehyde.

The compounds of the invention can be purchased or made by methods known in the art. One means to make such compounds is provided in U.S. Patent No. 5,089,509 which is hereby incorporated herein by reference.

The "retinoid composition" contains the retinoid compounds of the invention in amounts suitable for topical use on humans. Such compositions may be in the form of a gel, cream, lotion, ointment, cleanser or solution and include a variety of preservatives, carriers and other inactive or active ingredients.

As used herein, "therapeutically-effective amount" refers to that amount of a therapeutically-active retinoid necessary to administer to a human patient to treat psoriasis. Such amounts depend on the retinoid and its bioavailability but can range from about 0.01% to about 10% by weight, or preferably from about 0.025% to about 1-5 % by weight. For tazarotene, commercially available preparations of 0.05% and 0.1% are effective. Therapeutically-effective amounts can be readily determined by one of ordinary skill in the art.

As demonstrated by the following examples, surprisingly good results are obtainable using short-contact retinoid therapy. Not only does it appear that there is no loss of effectiveness of the active retinoid ingredient (as compared with conventional extended-contact therapy), but also that the effectiveness may be

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enhanced in some instances. Even more important, the adverse reactions are substantially reduced to tolerable or even negligible levels, thereby resulting in the ability and willingness of the user to adhere to the novel regimen. This combination of effects, i.e., equal or enhanced effectiveness, reduction in adverse reactions, and regimen adherence, yields surprisingly improved therapeutic efficacy.

EXAMPLE 1

Three patients were treated for psoriasis with short-contact tazarotene therapy for a period of at least six weeks. The contact period was from 30 seconds to 30 minutes followed by immediate rinsing. All three patients showed greater than 75% reduction in plaque thickness and scale. These results were significantly better thatn those seen in corresponding plaques which were either untreated (one patient) or treated with traditional phototherapy (two patients). One of 3 patients noted minor irritation.

Short-contact tazarotene therapy for psoriasis has also been used successfully on alternate-day and three-times-weekly schedules.

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CLAIMS

1. A method of treating psoriasis in a human patient comprising the steps of (1) topically applying an effective amount of a retinoid composition to the affected area of a patient's skin; (2) allowing said composition to remain in contact with the skin for a period of from about thirty seconds to about thirty minutes; and (3) rinsing said retinoid composition from said affected area.

2. The method according to Claim 1 wherein said composition remains in contact with the skin for a period of from about two to about ten minutes.

3. The method according to Claim 1 wherein said retinoid composition comprises tretinoin, tazarotene or adapalene as the topically-active retinoid.

4. The method according to Claim 2 wherein said retinoid composition comprises tretinoin, tazarotene or adapalene as the topically-active retinoid.

5. The method according to Claim 3 wherein said topically-active retinoid is present in an amount of about 0.01% to about 10% by weight.

6. The method according to Claim 4 wherein said topically-active retinoid is present in an amount of about 0.01% to about 10% by weight.

7. The method according to any one of Claims 1-6, wherein steps (1) to (3) are carried out at least 3 times per week.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03457

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/44
US CL :514/299

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)

U.S. : 514/299

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)

STN, CAPLUS, MEDLINE, SCISEARCH, EMBASE, TOXLINE, JAPIO, EUROPATFUL, BIOSIS
search terms; tazarotene, skin, acne, psoriasis, retinoid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,719,195 A (BRAIMAN) 17 Feburary 1998, see entire abstract and claims.	1-7
A	US 5,516,793 A (DUFFY) 14 May 1996, see claims .	1-7
A	US 5,650,279 A (NAGPAL et al) 22 July 1997, see abstract.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

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(54) Title: BENZOQUINOLIZINE-2-CARBOXYLIC ACID-CONTAINING COMPOSITIONS

(57) Abstract: This invention relates to topical compositions of an antibacterial benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in hitherto undescribed pharmaceutical compositions, or as an ingredient in novel combination with at least one agent selected from a retinoid, an antifungal agent, another antibacterial compound and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

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BENZOQUINOLIZINE-2-CARBOXYLIC ACID-CONTAINING COMPOSITIONS

FIELD OF THE INVENTION

This invention relates to topical compositions of an antibacterial benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in hitherto undescribed pharmaceutical compositions, or as an ingredient in novel combination with at least one agent selected from a retinoid, an antifungal agent, another antibacterial compound and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

BACKGROUND OF THE INVENTION

Topical compositions are useful for a wide range of dermal infection-originating disorders, ranging from those that are skin-related to those that are related to specific body parts, such as ophthalmic, otic and nasal disorders. The incidence and epidemiology of these different disorders is well documented in the scientific and patent literature.

The use of a benzoquinolizine-2-carboxylic acid antibacterial to treat infections represents the current state of the art in the field of dermal pharmaceutical compositions and methods of treatment. For example, a topical dermal composition containing the benzoquinolizine-2-carboxylic acid, RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, is marketed by Wockhardt Limited, India under the name NADOXIN™(Nadifloxacin 1 %) Cream.

Although RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, from chemical considerations, belongs to the class of benzoquinolizine-2-carboxylic acids, it is classified from considerations of its antibacterial mode of inhibition of one or both of the essential Type II DNA topoisomerase enzymes viz. DNA gyrase and Topoisomerse IV, and its common quinolone core moiety, as a quinolone antibacterial, with its given name analogous in terminology to drugs like ciprofloxacin and levofloxacin.

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RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid has also been utilized in other dermal antibiotic compositions:

ACUATIM™ Cream, Otsuka Pharmaceuticals, Japan
ACUATIM™Lotion, Otsuka Pharmaceuticals, Japan

In the field of ophthalmic pharmaceutical formulations and methods of treatment, the current state of the art embraces the use of quinolone antibiotics such as ciprofloxacin, ofloxacin, norfloxacin, and lomefloxacin as outlined in US Patent 6,395,476 and WO 0018404 (PCT /US 99/22625), the contents of which are incorporated herein by reference.

Among benzoquinolizine-2-carboxylic acids reported to have therapeutically and/or prophylactically useful antibiotic, in particular antibacterial effect are those illustratively disclosed in the following patents and patent applications, each of which is individually incorporated herein by reference:

US Patent No. 4,399,134;
US Patent No. 4,552,879;
US Patent 6,514,986;
US Patent 6,608,078
IN 188847;
Chem. Pharm. Bull. 44 (1996), 642-5;
US Application No. 09/566,875 filed on May 8, 2000;
PCT Application No. PCT/IN00/00054 filed on May 8, 2000;
US Application No. 09/640,947 filed on August 17, 2001;
PCT Application No. PCT/IN00/00111 filed on Nov. 2000;
PCT Application No. PCT/IN01/00097 filed on May 3, 2001 (WO 0185095);
PCT Application No. PCT/IN01/00100 filed on May 8, 2001 (WO 185728);
US Patent 6,664,267;
PCT Application No. PCT/IN02/00123 filed on May 28, 2002 (WO 03099815);
PCT Application No. PCT/US02/12790 filed on April 24, 2002 and
US Application No. 2002/0187193 A1 filed on December 12, 2002.

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Compounds disclosed in the above-cited Indian and US patents and patent applcations include for instance,

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

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid also referred to herein as S-(-)-nadifloxacin and hydrates thereof, and

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, also referred to herein as S-(-)-nadifloxacin arginine salt and polymorphs and hydrates thereof.

RS-nadifloxacin and S-nadifloxacin, in particular, exhibit strong antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria, resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), quinolone-resistant *Staphylococcus aureus,* coagulase negative staphylococci, such as methicillin-resistant *Staphylococcus epidermidis* (MRSE), enterococci, betahemolytic streptococci and viridans group of streptococci, mycobacteria and newly emerging nosocomial pathogens such as *Chryseobacterium meningosepticum,* and Gram-negative pathogens such as *E.coli, Klebsiella, Proteus, Serratia, Citrobacter* and *Pseudomonas*. Recently, it has also been shown that S-(-)-nadifloxacin, in particular exhibits potent antibacterial activity against glycopeptide intermediate *S. aureus* (GISA),vancomycin intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA).

Many Gram-positive organisms have developed significant levels of resistance to other antibiotics. About 65% of all cases of bacterial keratitis and about 85% of all cases of bacterial conjunctivitis are attributable to infection by gram-positive organisms such as those listed above. The causative organism of acne vulgaris is *Propionibacterium acnes*. The incidence of acne vulgaris is very high, specially among adolescents. Among new emerging diseases are pyoderma gangrenosum and necrotising fascitis. Pyoderma gangrenosum is a chronic destructive ulcerating wound disorder of unknown etiology, and pathophysiology. *S. aureus* is most often the infecting microorganism. Necrotising fascitis is a life threatening bacterial

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infection causing necrosis of the fascia, underlying skin and vasculature. It progresses rapidly, has a frightening 74% mortality and a high risk of systemic activity. The Group A beta-hemolytic streptococci (GABHS) are frequently identified in necrotising fascitis. Gonzalez M., Necrotising fascitis and gangrene of the upper extremity. Hand Clinics, 14(4), 635-645 (1998); Misago N. et.al., Necrotising fascitis due to group A *Streptococci*: A clinicopathology study of six patients. J. of Dermatology, 23, 876-883(1996). Another type of nacrotising fascitis involves several bacteria occurring with facultative and anaerobic bacteria. However, the infection is commonly polymicrobial in etiology (Geeham D M & Pemberton L B, Management of Wound Infection in the I.C.U. Critical Care Nursing Quarterly, 69-77, 1997, November), other causative enzymes including *Clostridium, Peptococcus E.coli Pseudomonas, S. pyogenes S. aureus, S. epidermidis, S. marcescens* (Douglas M, Necrotising fascitis: A nursing perspective, J. of Advanced Nursing, 24, 161-66, (1996);Gillen P B, Necrotising fascitis: Early recognition and aggressive treatment remain important, J. of Wound and Ostomy Care Nursing, 22 (5), 219-221, 1995). Bacterial resistance to antibiotics is an increasingly recurrent phenomenon. The need for pharmaceutical compositions specifically to treat infections arising from such emerging and resistant microorganisms thus assumes urgent significance.

The etiology of acne, its epidemiology, its psychosocial effects leading to impaired academic and social functioning, its effects on employment status, its consequences on the overall well-being and quality of life of the patient with acne, and the aims of treating it are described in US 5,543,417 and 6,365,623 B1 and references contained therein, all of which are included herein by reference. Acne is a disease with multifactorial pathogenesis including among other factors that of proliferation of *Propionibacterium acnes*. Among conventional topical treatments such as the antibiotics erythromycin and esters thereof, neomycin, clindamycin and esters thereof, tetracycline or the more recent RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, and anti-seborrhoeic or keratolytic agents such as benzoyl peroxide, salicylic acid, azelaic acid used for the removal of comedones in acne, are the topical retinoids such as tretinoin, isotretinoin and those listed in US Patent 4,717,720, US Patent 5,587,367 and US Patent 6,462,064 and references contained therein, all of which are included herein by reference. US patent 5,587,367 discloses a pharmaceutical or cosmetic dermal composition containing a combination of a retinoid with a second agent, such a second agent being a sterol.

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The compositions of this invention comprise a combination of an antibacterial benzoquinolizine-2-carboxylic acid such as herein described and a retinoid such as herein described resulting in a synergistic effect for the treatment of epidermic keratinization disorders, epithelial or epidermic proliferation disorders and/or disorders of the sebaceous function, for instance disorders selected from the group consisting of acne vulgaris, comedonic or polymorphic acne, acne rosaria, nodulocystic acne, acne conglobata, senile acne and secondary acnes.

Allergic inflammatory conditions of the skin are manifested by macules, papules or raised wheals involving part/s of the body. At cellular level there is a breakdown of phospholipids in the cell membrane and this gives rise to mediators like leukotrienes, platelet activating factor, prostaglandins and histamine. A steroid is generally administered to alleviate the symptoms of erythema, the immune response and the related itching which are normally associated with the above-mentioned group of bacterially-infected or invaded immunologic and/or allergic inflammatory dermal disorders. It is undesirable to use steroids alone for topical treatment for extended periods of time. Steroids can penetrate the skin and cause undesirable effects, including skin atrophy, suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, glycosuria, hyperglycemia, etc. Combinations of antibacterials and steroids are disclosed in US Pat. Nos. 4,604,384, WO 2002/039993, WO 02/30395 A1, WO 00/18404, US 6,395,746, and WO 00/18404.

Fungal diseases refer to fungal infections, including yeast infections, of keratinized and non-keratinized epithelial tissues, for example skin, nails, mucosa and the like and includes tinea pedis, tinea capitis, tinea corporis, tinea versicolor, nail fungal diseases (distal subungual onychomycosis caused by dermatophyte infection), scalp disorders, tinea cruris, and candidiasis (cf. US 6,075,056, incorporated herein by reference). Antifungal agents are useful in treating dermatophytoses such as trichophytid, endodermophytosis, favid and deepseated trichophytid and fungal infections such as mucocutaneous mycosis and deep-seated candidiasis (cf. WO 2000062776, incorporated herein by reference).

None of the references cited above specifically contemplates formulating a benzoquinolizine-2-carboxylic acid antibiotic in topical combination compositions using one or more ingredients selected from the group of a retinoid, an antibacterial, a steroid / non-steroid antiinflammatory agent and/or an antifungal agent.

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None of the references cited above specifically contemplates formulating a benzoquinolizine-2-carboxylic acid antibiotic in a combination therapy or coformulation of a benzoquinolizine-2-carboxylic acid antibacterial agent having a high degree of activity against gram-positive bacterial with one or more antibacterial agents effective against gram-negative bacteria and/or with a retinoid, steroid/non-steroid antiinflammatory agent and/or antifungal agent.

SUMMARY OF THE INVENTION

It is an aspect of this invention to provide topical compositions of an antibacterial benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in pharmaceutical compositions, or as an ingredient in combination with at least one agent selected from the group of a retinoid, an antifungal agent, an antibacterial and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention, any benzoquinolizine-2-carboxylic acid, antimicrobial drug or one of its chiral isomers i.e. one having a benzoquinolizine-2-carboxylic acid moiety as part of its chemical structure, can be formulated in a composition either as a single ingredient or in combination with one or more ingredients selected from the group of retinoid, an antifungal agent, an antibacterial and/or a steroid/non-steroid anti-inflammatory agent and one or more acceptable excipients, carriers, or diluents.

One embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal compositions with at least one adjunct retinoid ingredient resulting in a synergistic effect for the treatment of epidermic keratinization disorders, epithelial or epidermic proliferation disorders and/or disorders of the sebaceous function, for instance disorders selected from the group consisting of acne vulgaris, comedonic or polymorphic acne, acne rosaria, nodulocystic acne, acne conglobata, senile acne and secondary acnes.

Another embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal compositions with at least one steroid ingredient resulting in a synergistic

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effect for the treatment of bacterially infected or invaded immunologic and/or allergic inflammatory disorders, for instance selected from the group consisting of contact dermatitis, seborrhoeic dermatitis, erythema multiformae, pyodermic-related wounds and infective eczema and ophthalmic, otic or nasal disorders. The formulation of this invention has the advantages of combining an agent useful for treating the dermal and other body part/s bacterial diseases and disorders with a steroid capable of reducing the associated inflammation, with the ability to rapidly eradicate bacterial infections and eliminate the symptoms thereof, and as a consequence minimize the risk of undesirable side effects. Such a formulation would ideally deliver the antibacterial agent and the steroid to the skin and other body part/s, and maintain the combination on the skin and other body part/s for the period of time necessary to effect treatment, but minimize the penetration of the skin or other body part/s with respect to the active ingredients, thus avoiding the potential steroid effects noted above.

Still another embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal and other body part/s compositions with at least one antifungal agent ingredient resulting in a synergistic effect for the treatment of bacterially infected fungal diseases.

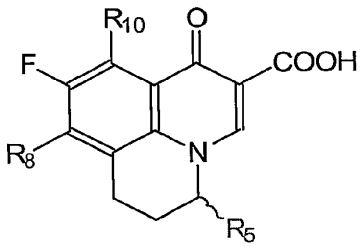
An antifungal agent is any agent that prevents the growth of or kills a fungal organism such as antifungal polyene macrolides such as amphotericin B, and nystatin, azole antifungal agents such as clotrimazole, miconazole, and ketoconazole, arylmethylamine antifungal agents such as butenafine and terbinafine (cf. EP 0310122B1, incorporated herein by reference), fluorinated pyrimidines, halogenated phenolic ethers, thiocarbamates, allylamines, benzylamines. In addition, antifungal agents can be agents that interpolate fungal cell wall components or act as cell wall inhibitors. Specific antifungal agents within the scope of the invention include, without limitation, the squalene epoxidase inhibitor, butenafine, and the ergosterol biosynthesis inhibitor, miconazole.

Still another embodiment of this invention relates to an antibacterial benzoquinolizine-2-carboxylic acid-containing dermal and other body part/s compositions with at least one antifungal agent ingredient and at least one steroid resulting in a synergistic effect for the treatment of bacterially infected, inflammatory fungal diseases. WO 99/20261 (incorporated herein by reference) describes inflammation of mucosal tissue, fungus-induced mucositis and rhinositis, other fungus-induced mucositis conditions such as chronic otitis media, and methods

and materials for treating them. Topical compositions are described for psoriatic infections (WO 9949835, incorporated herein by reference), and for cutaneous mycosis including candidiasis, vulvitis, etc., (JP 07233088 (incorporated herein by reference).

The subject antibiotic benzoquinolizine-2-carboxylic acid compounds, including but not limited to RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-nadifloxacin, S-nadifloxacin arginine salt, can be formulated as a gel or cream for topical application to skin, or they can be formulated as an ointment or gel; or eye drops for application to a mammalian eye.

Preferred benzoquinolizine-2-carboxylic acid are compounds having Formula-I

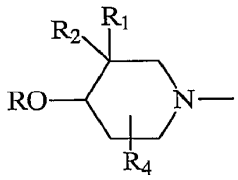


Formula-II

Preferably R_5 is C_{1-6} alkyl, and more preferably R_5 is CH_3, as a mixture of enantiomers or in a stereochemical orientation .

Preferably 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.

More preferably R_8 is



wherein

R is hydrogen, C_1-C_6 alkyl, glycosyl, or aralkyl such as benzyl, or R is C_1-C_6 alkanoyl such as acetyl, propionyl, or pivaloyl; or aminoalkanoyl such as amino acid residues derived from one of the 20 naturally occurring amino acids viz. alanine, arginine, asparagine, aspartic acid,

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cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, or the optically active isomers thereof, or the racemic mixtures thereof, or R is $C_6H_{11}O_6$, PO_3H_2 or SO_3H thus giving respectively the gluconic acid, phosphoric acid and sulfonic acid ester derivatives of the compounds;

R_1 and R_2 are the same or different and represent H, C_{1-4} alkyl, aralkyl, aminoalkyl, trifluoroalkyl, or halogen;

R_4 is selected from H, C_{1-4} alkyl, CF_3, phenyl, or F and R_4 is present at one or more of the positions of 2-, 4-, 5-, or 6- of the piperidine ring;

R_{10} is H, C_{1-5} alkyl, amino, alkylamino, or acylamino;

or an optical isomer, diastereomer or enantiomer thereof, or a polymorph, pseudopolymorph, or prodrug thereof or a pharmaceutically acceptable salt or hydrate thereof.

"Optical isomer", "stereoisomer", and "diastereomer" as referred to herein have the standard art recognized meanings.

Examples of preferred benzoquinolizine-2-carboxylic acid are compounds selected from RS-(±)-, R-(+)- or 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 polymorphic forms thereof, RS-(±)-, R-(+)- or 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, RS-(±)-, R-(+)- or S-(-)- 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-{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, 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, S-(-)-9-fluoro-6,7-dihydro-8-(3-ethyl-4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-

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benzo[i,j]quinolizine-2-carboxylic acid (mixture of cis racemate and trans racemate) and pure stereoisomers 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, also referred herein as RS-(±)-nadifloxacin,

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid also referred to herein as S-(-)-nadifloxacin, and

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, also referred to herein as S-(-)-nadifloxacin arginine salt.

Benzoquinolizine compounds used in compositions of the invention can be prepared by a process known per se, by processes described in the patents included herein by reference disclosing such drugs.

US Patent No. 4,399,134
US Patent No. 4,552,879
US Patent 6,514,986;
US Patent 6,608,078;
US Application No. 09/566,875
US Application No. 09/640,947
US Application No. 10/156,685

Antibiotics that can be used in combination with an antibacterial benzoquinolizine-2-carboxylic acid compound may include but are not limited to:
Polymyxin Sulphate(Gram -ve), Neomycin, Bacitracin, Trimethoprin, Tobramycin, Terramycin, Sulfacetamide, Cefazolin, Gramicidin and Colistin Sulphate(Gram -ve).

Retinoids, antiacne agents, steroids (glucocorticoids) and antifungal agents that can be used in the compositions of this invention include but are not limited to:
Retinoids: Benzoyl peroxide, Dichloroacetic acid, Glutaraldehyde, Resorcinol, Retinoic acid and Salicylic acid.

Antiacne: Adapalene, Algestone acetophenide, Azelaic acid, Benzoyl peroxide, Cioteronel,

Cyproterone, Isotretinoin, Motretinide, Resorcinol, Retinoic acid, Tretinoin, Tazarotene and Tioxolone.

Glucocorticoid: 21-acetoxypregnnolone, Alclometasone, Algestone, Amcinonide, Beclomethasone, Betamethasone, Budesonide, Chloroprednisone, Ciclesonide, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Corticosterone, Cortisone, Cortivazol, Deflazacort, Desonide, Desoximetasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate, Enoxolone, Fluazacort, Flucloronide, 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, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 21-diethylaminoacetate, Prednisolone sodium phosphate, Predisone, prednival, Prednylidene, Rimexolone, Tixocortol, Triamcinolone, Triamcinoloneacetonide, Triamcinolone benetonide, Triamcinolone hexacetonide.

Antifungal (Antibiotics): Polyenes: Amphotericin, Candicidin, Dermostatin, Filipin, Fungichromin, Hachimycin, Hamycin, Lucensomycin, Mepartricin, Natamycin, Nystatin, Pecilocin, Perimycin, Azaserine, Caspofungin, Griseofulvin, Oligomycins, Pyrrolnitrin, Siccanin, Tubercidin, Viridin.

Antifungal (Synthetic): Allylamines: Butenafine, Naftifine, Terbinafine
Imidazoles: Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, Clotrimazole, Econazole, Enilconazole, Fenticonazole, Flutrimazole, Isoconazole, Ketoconazole, Lanoconazole, Miconazole, Neticonazole, Omoconazole, Oxiconazole nitrate, Sertaconazole, Sulconazole, Tioconazole.
Thiocarbamates: Liranaftate, Tolciclate, Tolindate, Tolnaftate
Triazoles: Fluconazole, Itraconazole, Posaconazole, Saperconazole, Terconazole, Voriconazole.

Others: Acrisorcin, Amorolfine, Biphenamine, Bromosalicylchloranilide, Buclosamide, Calcium propionate, Chlorphenesin, Ciclopirox, Cloxyquin, Coparaffinate, Diamthazole dihydrochloride, Exalamide, Flucytosine, Hexetidine, Loflucarban, Nedocromil sodium, Nifuratel, Potassium

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iodide, Propionic acid, Pyrithione, Salicylanilide, Sodium propionate, Sulbentine, Tenonitrozole, Triacetin, Undecylenic acid, Zinc propionate

The preferred retinoid is adapalene.
The preferred steroid is clobetasol or mometasone, in particular, clobetasol propionate.
The preferred antifungal agent is butenafine.

The compositions of this invention contain from about 0.1 to 10% by weight of the composition of an antimicrobial benzoquinolizine-2-carboxylic acid compound.
Preferably the amount of the an antimicrobial benzoquinolizine-2-carboxylic acid compound in the composition is 1% by weight of the total weight of the composition. More preferably, the amount of the an antimicrobial benzoquinolizine-2-carboxylic acid compound in the composition is 0.5% by weight of the total weight of the composition.

Preferably, the amount of the retinoid present in a composition of this invention is 0.001 to 10.0% by weight relative to the total weight of the composition.
Preferably, the amount of the steroid present in a composition of this invention is 0.005-1.0% by weight relative to the total weight of the composition.
Preferably, the amount of the antifungal agent present in a composition of this invention is 0.1 to 10.0% by weight relative to the total weight of the composition.

The compositions of this invention may be in a physical form selected from concentrates, drops, pastes, ointments, creams, milks, pomades, powders, impregnated pads, tulles, solutions, gels, sprays, shampoos, lotions, suspensions, microspheres, nanospheres, lipidic vesicles, polymeric vesicles, polymeric patches or biological inserts.

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

In addition to the benzoquinolizine-2-carboxylic acid and/or one of its combination partners mentioned above, the compositions will also include a pharmaceutical vehicle compatible with an administration by a topical method (skin and mucous), ocular, otic or nasal or the other routes of administration described herein.

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For topical application, the pharmaceutical or cosmetic compositions of the invention comprise the vehicles and ingredients required to provide the composition, for example, in the form of ointments, creams, milks, pomades, powders, impregnated pads, solutions, gels, sprays, shampoos, washing lotions or even suspensions, microspheres or nanospheres, lipidic or polymeric vesicles or polymeric patches.

For ocular administration, the composition of the invention is provided in the form of eyedrops or eyewashes.

In those embodiments of the present invention wherein the pharmaceutical composition is in the form of ointments, creams, lotions, gels and the like for dermal application, the vehicle may also contain other pharmaceutically acceptable excipients known in the art for pharmaceutical compounding such as for example, penetration enhancers, humectants and/or moisturizers, preservatives, opacifiers, fragances, color additives, counter-irritants and the like.

The penetration enhancers, for improved transepidermal or percutaneous delivery of drug, suitable for the present invention include terpenes, terpene alcohols, essential oils, surfactants, and the like. Some such examples include d-limonene, terpinen-4-ol, menthone, 1,8-cineole, 1-pinene, α-terpineol, carveol, carvone, pulegone, eucalyptol, peppermint oil, sorbitan esters, polysorbates, sodium lauryl sulphate, and the like.

Suitable humectants and/or moisturizers that may be used in the present invention include polyhydroxy alcohols such as sorbitol, glycerin, hexanetriol, butanediol, mannitol, glucose, ethylene glycol, propylene glycol, and the like.

Preservatives such as methylparaben, propylparaben, phenoxyethanol, benzyl alcohol, bromopol, chlorocresol, thiomersal, benzalkonium chloride, and the like may be added to the compositions to inhibit microbial activity.

Opacifiers, such as behenic acid, glycol distearate, lard glycerides, polyethylene glycol esters, and the like; fragrances such as amyl salicylate, panisaldehyde, anisylalcohol, peppermint oil, wintergreen oil, and the like; colour additives such as quinoline yellow, and the like; counter-irritants such as methyl salicylate, menthol and the like; and other pharmaceutical adjuvants may be added to the compositions of the invention.

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Antiforming agents such as simethicon and dimethicon may be added to the compositions.

In those embodiments of the present invention wherein the pharmaceutical composition is in the form of solutions, suspensions, ointments, gels and the like for ocular administration, the vehicle may also contain other ophthalmically acceptable excipients known in the art for pharmaceutical compounding such as for example, solvents, fillers, buffering agents, tonicity regulators, viscosity enhancers, lubricity components, chelating/sequestering agents, stabilizing agents, and the like.

As used herein, the term "ophthalmically acceptable" refers to an excipient which, at the concentration or amount in question, is compatible with ocular tissue and does not cause significant or undue detrimental effects when brought into contact with ocular tissue.
In those embodiments of the present invention wherein the pharmaceutical composition is intended for ocular administration, it may contain water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum-based jelly, ethyl oleate, isopropyl myristate, and the like as solvents; polyethylene glycols, carbowaxes, petroleum jelly and the like as a fillers; tromethamine, phosphate, borate, acetate, citrate buffers, and the like as a buffering agents; dextrose, potassium chloride, sodium chloride, and the like as a tonicity regulators; carbopol, ethyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose and the like as a viscosity enhancers; polyvinyl alcohol, polyvinylpyrrolidone, carbopol and the like as a lubricity components; ethylene diamine tetraacetic acid (EDTA), citric acid, tartaric acid, and the like as a chelating or sequestering agents; and antioxidants, for example, alkali metal metabisulfates, ascorbic acid, and the like as a stabilizing agent.

In an embodiment of the process of the present invention, the present compositions may be prepared using conventional techniques, for example, by formation of solutions, gels, suspensions, etc., using well known and conventional techniques. For a more detailed discussion of the preparation and administration of ophthalmic formulations see Remington's Pharmaceutical Sciences, 15 Ed., Pgs. 1489 to 1504 (1975) which is incorporated in its entirety herein by reference. Compositions of the present invention can also be prepared by processes known in the art, including by simple admixture, with agitation as appropriate, of the ingredients. The processes for preparing a composition of the invention are preferably conducted so as to provide a sterile product.

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According to an embodiment of the present invention, the container into which the dosage forms are dispensed could be made of glass, plastic, aluminum, and the like. In this connection, the container materials can contain substances that confer a particular protection on the contents, such as, for example, a protection from light or a protection from oxygen.

The invention also has for an object the use of the ingredients of the invention in the preparation of a pharmaceutical or cosmetic composition intended principally for the treatment or correction of epidermic keratinization disorders, any other disorder or any other functional defect or excess of epidermic or epithelial proliferation. The composition thus prepared can serve to treat the disorders mentioned above, having or not an inflammatory and/or immunoallergic component, comprising conjunctive tissue degeneration disorders and benign or malignant tumors, to combat against skin aging, to favor cicatrization or to improve the appearance of the skin of persons exhibiting keratinization disorders or suffering from seborrhea. The invention also has for an object the use of the ingredients of the invention in the preparation of a pharmaceutical composition intended for the treatment of ocular and periocular infections.

In particular, the combination described in the present invention is intended:

for the treatment of dermatologic ailments linked to a keratinization disorder causing differentiation and proliferation and principally for treating common acne, comedons, polymorphs, nodulokystic acne, conglobuta, senile acne, secondary acne such as solar, medicinal and professional acne;

for the treatment of other types of keratinization disorders, principally ichthyoses, ichthyosiform conditions, Darier malady, palmoplantary keratodermies, leucophasies and leucoplasiform conditions as well as lichen;

for the treatment of dermatologic ailments linked to a keratinization disorder having an inflammatory and/or immunoallergic component and principally, all forms of psoriasis, be they cutaneous, mucous or ungual, and even psoriasic rheumatism, or again cutaneous atopies, such as eczema;

for the treatment of other dermatologic disorders such as blistery dermatoses and collagen maladies;

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to prevent or heal scars of epidermic and/or dermic atrophy, induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;
for the treatment of certain ophthalmologic disorders, principally corneopathies; bacterial keratitis, corneal ulcers, bacterial conjunctivitis, associated or unassociated with allergy or itch to combat against disorders of the sebaceous function such as hyperseborrhea of acne or simple seborrhea;
to combat impetigo folliculitis, infected dermatitis, wounds and burns, pyoderma gangrenosum and necrotising fascitis.

The compositions of the invention are also useful in the cosmetic field, in particular in body hygiene, and also capillary hygiene (action against seborrhea).

Generally the composition for topical use is applied one or more times per day on the area to be treated. The number of times a time per day that the composition is applied depends on the severity of the condition and the advice of the physician.

In general, the present methods for treating mammalian eyes comprise administering to the mammalian eye a therapeutically effective amount of the present composition thereby providing an effective antibiotic in the mammalian eye, and, if a combination partner component is present in the composition, thereby reducing inflammation or pain in the mammalian eye. The present methods of use may involve any suitable administration step or steps to provide an effective amount of the composition to the mammalian eye. Such administering may include, but is not limited to, topical application to the eye, instillation into the eye, placing an insert into the cul-de-sac (space) between the eyeball and the eyelid and the like. Other conventional methods of administering compositions to the eye may be employed provided that the present compositions are administered so as to provide the benefits desired.

The present use methods may be considered to be curative and/or preventative when applied, presurgically or immediately post traumatically, that is before a microbial infection develops, or before inflammation and/or pain is apparent. The present use methods are effective to reduce the risk of the formation of such infections and to reduce the severity of any inflammation or pain which may develop.

The dosage level of the present composition depends, of course, on many factors, for example,

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the particular application involved, the particular active component or components employed, the concentration of the active component or components in the composition, the severity of the infection/inflammation/pain and the individuals response to the treatment. Such dosage can be easily determined by routine and well known techniques to achieve the desired results in the individual patient being treated.

The following non-limiting examples illustrate certain aspects of the present invention.

Example 1

This example illustrates the present invention in the form of a gel 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. The pharmaceutical composition of this example is given below in table 1:

Table 1

Ingredients	% weight of the Composition
Active antibacterial	1.00
Carbopol	1.20
Sodium hydroxide	0.112
Diethanolamine	0.36
Disodium edetate	0.10
Sodium sulfite anhydrous	0.05
Purified water	q.s. to 100.00

Sodium hydroxide, diethanolamine, sodium sulfite anhydrous and the active antibacterial ingredient were dissolved in purified water (Solution A). Carbopol was dispersed in 50% w/v aqueous solution of disodium edetate to which was added Solution A and mixed to form a gel.

Example 2

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 and adapalene. The pharmaceutical composition of this example is given below in table 2.

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Table 2

Ingredients	% Weight of the composition
Active antibacterial	1.00
Adapalene	0.10
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
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 of disodium edetate was also heated to 70°C and added to the above mixture under homogenization to form an emulsion. Dispersion of methyl paraben and propyl paraben in 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 following which the active antibacterial ingredient and adapalene were triturated with part quantity of cream and then mixed with entire quantity of cream. The cream was passed through triple roller mill prior to filling in the tubes.

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Example 3

This example illustrates the present invention in the form of a gel 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 and adapalene. The pharmaceutical composition of this example is given below in table 3.

Table 3

Ingredients	% weight of the Composition
Active antibacterial	1.00
Adapalene	0.10
Carbopol	1.20
Sodium hydroxide	0.112
Diethanolamine	0.36
Disodium edetate	0.10
Sodium sulfite anhydrous	0.05
N-methyl-2-pyrrolidone	2.50
Methyl paraben	0.18
Propyl paraben	0.02
Propylene glycol	5.00
Purified water	q.s. to 100.00

Sodium hydroxide, diethanolamine, sodium sulfite anhydrous and RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid were dissolved in purified water (Solution A). Adapalene was dissolved in n-methyl-2-pyrrolidone (Solution B). Methyl paraben and propyl paraben were dissolved in propylene glycol (Solution C). In a 50 % (w/v) aqueous solution of disodium edetate were added all the solutions A, B and C, one by one, and mixed to form a gel.

Example 4

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 and a steroid, clobetasol, propionate. The pharmaceutical composition of this example is given below in table 4.

Table 4

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Ingredients	% Weight of the composition
Active antibacterial	1.00
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
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. Dispersion 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, and the active antibacterial ingredient were triturated with part quantity of cream and then mixed with the entire quantity of cream. The cream was passed through triple roller mill prior to filling in the tubes.

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Example 5

This example illustrates the present invention in the form of a gel 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 and clobetasol propionate. The pharmaceutical composition of this example is given in below in table 5.

Table 5

Ingredients	% weight of the Composition
Active antibacterial	1.00
Clobetasol propionate	0.05
Carbopol	1.20
Sodium hydroxide	0.112
Diethanolamine	0.36
Disodium edetate	0.10
Propylene glycol	15.00
Sodium sulfite anhydrous	0.05
Methyl paraben	0.18
Propyl paraben	0.02
Purified water	q.s. to 100.00

Sodium hydroxide, diethanolamine, sodium sulfite anhydrous and the active antibacterial ingredient were dissolved in purified water (Solution A). Paraben was dissolved in propylene glycol (Solution B). Clobetasol propionate was dissolved in propylene glycol (Solution C). Carbopol was dispersed in an aqueous solution 50 % (w/v) of disodium edetate to which was added Solutions A, B and C, one by one, and mixed to form a gel.

Example 6

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 butenafine hydrochloride. The pharmaceutical composition of this example is given below in table 6.

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Table 6

Ingredients	% Weight of the composition
Active antibacterial	1.00
Butenafine Hydrochloride	1.00
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 45% (w/v) of disodium edetate was also heated to 70°C and added to the above mixture under homogenization to form an emulsion. Dispersion 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 butenafine hydrochloride were triturated with part quantity of cream

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