

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*

Serial No.: TBA

Filed: Herewith

For: METHODS OF PROVIDING
THERAPEUTIC EFFECTS USING
CYCLOSPORIN COMPONENTS

Examiner: TBA

Group Art Unit: TBA

Confirmation No. TBA

Customer No.: 51957

PRELIMINARY AMENDMENT

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

Dear Sir:

Prior to examining the above-referenced application, please amend the specification as described on page 2 of this paper, and please amend the claims as described on pages 3-6 of this paper. Remarks follow on page 7.

Amendments to the Specification

Please replace page 1, lines 5-10 of the specification filed herewith with the following amended paragraph:

This application is a continuation of copending U.S. Application Serial No. 13/961,835 filed August 7, 2013, which is a continuation of copending U.S. Application Serial No. 11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No. 10/927,857, filed August 27, 2004, ~~now abandoned,~~ which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which ~~is~~ are incorporated in ~~its~~ their entirety herein by reference.

Please replace page 4, line 25 – page 5, line 3 of the specification filed herewith with the following amended paragraph:

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea.

Amendments to the claims

The following list of claims will replace all previous versions of claims presented in this application:

1. – 36. (Canceled)

37. (New) A method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in increasing tear production.

38. (New) The method of Claim 37, wherein the emulsion further comprises a tonicity agent or a demulcent component.

39. (New) The method of Claim 38, wherein the tonicity agent or the demulcent component is glycerine.

40. (New) The method of Claim 37, wherein the emulsion further comprises a buffer.

41. (New) The method of Claim 40, wherein the buffer is sodium hydroxide.

42. (New) The method of Claim 37, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

43. (New) The method of Claim 37, wherein the emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

44. (New) The method of Claim 37, wherein the emulsion comprises Pemulen in an amount of about 0.05% by weight.

45. (New) The method of Claim 37, wherein the emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

46. (New) The method of Claim 45, wherein the buffer is sodium hydroxide.

47. (New) The method of Claim 37, wherein, when the emulsion is administered to an eye of a human in an effective amount in treating KCS, the blood of the human has substantially no detectable concentration of cyclosporin A.

48. (New) The method of Claim 42, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

49. (New) The method of Claim 37, wherein the emulsion is as substantially therapeutically effective as an emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

50. (New) The method of Claim 37, wherein the emulsion achieves at least as much therapeutic effectiveness as an emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

51. (New) The method of Claim 37, wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to an emulsion that contains only 50% as much castor oil.

52. (New) The method of Claim 37, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to an

emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

53. (New) The method of Claim 52, wherein the adverse events include side effects.

54. (New) A method of treating KCS, the method comprising the step of topically administering to an eye of a human an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

Pemulen in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the emulsion is effective in treating KCS.

55. (New) The method of Claim 54, wherein the buffer is sodium hydroxide.

56. (New) The method of Claim 54, wherein the tonicity component or the demulcent component is glycerine.

57. (New) The method of Claim 54, wherein, when the emulsion is administered to the eye of a human in an effective amount in treating KCS, the blood of the human has substantially no detectable concentration of the cyclosporin A.

58. (New) The method of Claim 54, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

59. (New) A method comprising:

administering an emulsion topically to the eye of a human having KCS, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

Pemulen in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water; and

wherein the emulsion is effective in increasing tear production in the human having KCS.

60. (New) The method of Claim 59, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

REMARKS

The applicants have canceled Claims 1-36 and have added Claims 37-60. Support for the limitations recited in the new claims may be found throughout the specification, and at least at page 4, line 25 – page 5, line 14, page 10, lines 1-7, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith. No new matter is added.

Support for the amendment to the specification at page 4, line 25 – page 5, line 3 may be found, at least, in U.S. Patent Nos. 5,474,979 and 6,254,860, which were previously incorporated by reference in the present application specification at page 1, lines 18-21. The amendment contains no new matter.

The claims of the present application may vary in scope from the claims pursued in the parent applications. To the extent any prior amendments or characterizations of the scope of any claim, or the specification, or referenced art could be construed as a disclaimer of any subject matter supported by the present disclosure, the Applicants hereby rescind and retract such disclaimer.

Specifically, the Applicants would like to bring to the Examiner's attention comments made in the Response filed on June 15, 2009 in U.S. Patent Application Serial No. 10/927,857 (now abandoned) and comments made in the Amendment filed on June 15, 2009 in U.S. Patent Application Serial No. 11/897,177 (currently pending) regarding U.S. Patent No. 5,474,979 and the present application specification. Since these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims.

The Commissioner is hereby authorized to charge any fees required or necessary for the filing, processing or entering of this paper or any of the enclosed papers, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

/Laura L. Wine/

Laura L. Wine
Attorney of Record

Date: August 14, 2013

Docket No. 17618CON7B (AP)

Registration Number 68,681

Please direct all inquiries and correspondence to:

Laura L. Wine, Esq.

Allergan, Inc.

2525 Dupont Drive, T2-7H

Irvine, California 92612

Tel: (714) 246-6996 Fax: (714) 246-4249

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	
<p>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.</p>		

Secrecy Order 37 CFR 5.2

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor 1					<input type="button" value="Remove"/>
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Andrew		Acheampong		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Irvine	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	16 Wintergreen				
Address 2					
City	Irvine	State/Province	CA		
Postal Code	92604	Country i	US		

Inventor 2					<input type="button" value="Remove"/>
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Diane	D.	Tang-Liu		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Las Vegas	State/Province	NV	Country of Residence i	US

Mailing Address of Inventor:

Address 1	3726 Las Vegas Blvd S. Unit 3303 W				
Address 2					
City	Las Vegas	State/Province	NV		
Postal Code	89158	Country i	US		

Inventor 3					<input type="button" value="Remove"/>
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	James	N.	Chang		
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	17618CON7B (AP)	
		Application Number		
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			

City	Newport Beach	State/Province	CA	Country of Residence i	US
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Mailing Address of Inventor:

Address 1	36 Cervantes				
Address 2					
City	Newport Beach	State/Province	CA		
Postal Code	92660	Country i	US		

Inventor 4

Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	F.	Power	

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

City	Hubert	State/Province	NC	Country of Residence i	US
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Mailing Address of Inventor:

Address 1	202 Fox Way N				
Address 2					
City	Hubert	State/Province	NC		
Postal Code	28539	Country i	US		

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

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Correspondence Information:

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 An Address is being provided for the correspondence information of this application.

Customer Number	51957		
Email Address	patents_ip@allergan.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
Attorney Docket Number	17618CON7B (AP)	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

Publication Information:

<input type="checkbox"/>	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
<input type="checkbox"/>	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.

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Customer Number	51597		

Domestic Benefit/National Stage Information:

<p>This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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.</p>			
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13961835	2013-08-07
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13961835	Continuation of	11897177	2007-08-28
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11897177	Continuation of	10927857	2004-08-27
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10927857	non provisional of	60503137	2003-09-15
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

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(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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

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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.

Authorization to Permit Access:

Authorization to Permit Access to the Instant Application by the Participating Offices

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

If 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 World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

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			<input type="button" value="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.			
<input type="button" value="Clear"/>			
<input checked="" type="radio"/> Assignee	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Joint Inventor	
<input type="radio"/> Person to whom the inventor is obligated to assign.		<input type="radio"/> Person who shows sufficient proprietary interest	
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Name of the Deceased or Legally Incapacitated Inventor : <input type="text"/>			
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	Allergan, Inc.		
Mailing Address Information:			
Address 1	2525 Dupont Drive		
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

Email Address	patent_ip@allergan.com
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Non-Applicant Assignee Information:

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Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section 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), as the patent application publication will include the name of the applicant(s).

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Signature	/Laura L. Wine/		Date (YYYY-MM-DD)	2013-08-14	
First Name	Laura	Last Name	Wine	Registration Number	68681

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	17618CON7B (AP)
	Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

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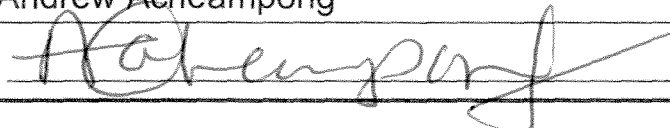
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements 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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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS Docket No.: 17618CON7(AP)
<p>As the below named inventor, I hereby declare that:</p> <p>This declaration is directed to: <input type="checkbox"/> The attached application, or <input checked="" type="checkbox"/> United States application or PCT international application number <u>13/961,835</u> filed on <u>8/7/2013</u>.</p> <p>The above-identified application was made or authorized to be made by me.</p> <p>I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.</p> <p>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.</p> <p style="text-align: center;">WARNING:</p> <p>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.</p>	
<p>LEGAL NAME OF INVENTOR</p> <p>Inventor: <u>Andrew Acheampong</u> Date (Optional): _____</p> <p>Signature: </p>	
<p>Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.</p>	

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.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS Docket No.: 17618CON7(AP)
-------------------------------	--

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 13/961,835
8/7/2013
 filed on _____.

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: DIANE TANG-LIU Date (Optional) : _____

Signature: 

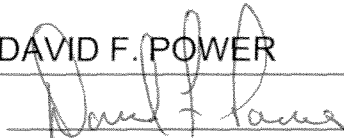
Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

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.

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.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS Docket No.: 17618CON7(AP)
<p>As the below named inventor, I hereby declare that:</p> <p>This declaration is directed to: <input type="checkbox"/> The attached application, or <input checked="" type="checkbox"/> United States application or PCT international application number <u>13/961,835</u> filed on <u>8/7/2013</u>.</p> <p>The above-identified application was made or authorized to be made by me.</p> <p>I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.</p> <p>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.</p> <p style="text-align: center;">WARNING:</p> <p>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.</p>	
<p>LEGAL NAME OF INVENTOR</p> <p>Inventor: <u>DAVID F. POWER</u> Date (Optional) : _____</p> <p>Signature: <u></u></p>	
<p>Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.</p>	

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.

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.

SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	Methods of Providing Therapeutic Effects Using Cyclosporin Components Docket No.: 17618CON7(AP)						
This statement is directed to:							
<input type="checkbox"/> The attached application,							
OR							
<input checked="" type="checkbox"/> United States application or PCT international application number <u>13/961,835</u> filed on <u>8-7-13</u>							
LEGAL NAME of inventor to whom this substitute statement applies:							
(E.g., Given Name (first and middle (if any)) and Family Name or Surname)							
James N. Chang							
Residence (except for a deceased or legally incapacitated inventor):							
City	Newport Beach	State	CA	Country	US		
Mailing Address (except for a deceased or legally incapacitated inventor):							
36 Cervantes							
City	Newport Beach	State	CA	Zip	92660	Country	US
I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.							
The above-identified application was made or authorized to be made by me.							
I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.							
Relationship to the inventor to whom this substitute statement applies:							
<input type="checkbox"/> Legal Representative (for deceased or legally incapacitated inventor only),							
<input checked="" type="checkbox"/> Assignee,							
<input type="checkbox"/> Person to whom the inventor is under an obligation to assign,							
<input type="checkbox"/> Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or							
<input type="checkbox"/> Joint inventor.							

[Page 1 of 2]

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.

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.

SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- Inventor is deceased,
 Inventor is under legal incapacity,
 Inventor cannot be found or reached after diligent effort, or
 Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.
OR
 An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

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.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: **Debra D. Condino** *COMPANY: ALLERGAN, INC. (ASSIGNOR)*
TITLE: ASSISTANT SECRETARY Date (Optional):

Signature: *D Condino*

Residence (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	Irvine	State	CA	Country	US
------	--------	-------	----	---------	----

Mailing Address (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

2525 Dupont Drive-T2-7H

City	Irvine	State	CA	Zip	92612	Country	US
------	--------	-------	----	-----	-------	---------	----

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

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.

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
 UNDER 37 CFR 1.102(e)** (Page 1 of 1)

First Named Inventor:	Andrew Acheampong	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.
2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.
3. The applicable box is checked below:

I. Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
 ---OR---
 (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Laura L. Wine/	Date August 14, 2013
Name (Print/Typed) Laura L. Wine	Practitioner Registration Number 68681

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*

*Total of 1 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.

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			
First Named Inventor/Applicant Name:	Andrew Acheampong			
Filer:	Laura Lee Wine			
Attorney Docket Number:	17618CON7B (AP)			
Filed as Large Entity				
Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Claims in Excess of 20	1202	4	80	320
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				6350

Electronic Acknowledgement Receipt

EFS ID:	16592863
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine
Filer Authorized By:	
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	14-AUG-2013
Filing Date:	
Time Stamp:	18:36:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$6350
RAM confirmation Number	6005
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON7B_SPEC.pdf	4359979 dcc61d22d9e349761eb22baaa348b5da22224204	yes	34

Multipart Description/PDF files in .zip description					
Document Description		Start	End		
Specification		1	28		
Claims		29	33		
Abstract		34	34		

Warnings:

Information:

2	Miscellaneous Incoming Letter	17618CON7B_POA.pdf	1931210 41409d37687184bf88bd42261199ec4036e34dd	no	2
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Warnings:

Information:

3	Power of Attorney	New_POA.pdf	1822911 054720bcc55afbbeb1191959b4661f3a266bec	no	1
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Warnings:

Information:

4		17618CON7B_Preliminary_Amendment.pdf	108252 9175467458a15cbfc03beda9d50d79f6d6ddf80a	yes	8
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Multipart Description/PDF files in .zip description					
Document Description		Start	End		
Preliminary Amendment		1	1		
Specification		2	2		
Claims		3	6		
Applicant Arguments/Remarks Made in an Amendment		7	8		

Warnings:

Information:					
5	Application Data Sheet	17618BCON7_ADS.pdf	1505532 f2899510834b464400f78a88b310171bd4e d4d61	no	8
Warnings:					
Information:					
6	Oath or Declaration filed	Dec17618CON7.pdf	5939071 681e32a3f4e5b622e8564573b8ff862e448f 08b8	no	6
Warnings:					
Information:					
7	TrackOne Request	PrioritizedExamination-17618C ON7B.pdf	153242 706cb46a3c4e701dbc5afd9a787175c6862 6917d	no	2
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	41862 a6662e5523531cc99da462abfd5fe068c514 5cfe	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			15862059		

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.

Electronic Acknowledgement Receipt

EFS ID:	16592863
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine
Filer Authorized By:	
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	14-AUG-2013
Filing Date:	
Time Stamp:	18:36:10
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON7B_SPEC.pdf	4359979 dcc61d22d9e349761eb22baaa348b5da22224204	yes	34

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	28
Claims	29	33
Abstract	34	34

Warnings:

Information:

2	Miscellaneous Incoming Letter	17618CON7B_POA.pdf	1931210 41409d37687184bf88bd42261199ec4036e34dd	no	2
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3	Power of Attorney	New_POA.pdf	1822911 054720bccc55afbbefb1f91959b4661f3a266bec	no	1
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4		17618CON7B_Preliminary_Amendment.pdf	108252 9175467458a15cbfc03beda9d50d79f6d6ddf80a	yes	8
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Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	6
Applicant Arguments/Remarks Made in an Amendment	7	8

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Information:					
5	Application Data Sheet	17618BCON7_ADS.pdf	1505532 f2899510834b464400f78a88b310171bd4e d4d61	no	8
Warnings:					
Information:					
6	Oath or Declaration filed	Dec17618CON7.pdf	5939071 681e32a3f4e5b622e8564573b8ff862e448f 08b8	no	6
Warnings:					
Information:					
7	TrackOne Request	PrioritizedExamination-17618C ON7B.pdf	153242 706cb46a3c4e701dbc5afd9a787175c6862 6917d	no	2
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8	Fee Worksheet (SB06)	fee-info.pdf	41862 a6662e5523531cc99da462abfd5fe068c514 5cfe	no	2
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METHODS OF PROVIDING THERAPEUTIC EFFECTS
USING CYCLOSPORIN COMPONENTS

5 Related Application

This application is a continuation of U.S. Application
Serial No. 10/927,857, filed August 27, 2004, which claimed
the benefit of U.S. Provisional Application No. 60/503,137
filed September 15, 2003, which is incorporated in its
10 entirety herein by reference.

Background of the Invention

The present invention relates to methods of providing
desired therapeutic effects to humans or animals using
15 compositions including cyclosporin components. More
particularly, the invention relates to methods including
administering to an eye of a human or animal a
therapeutically effective amount of a cyclosporin component
to provide a desired therapeutic effect, preferably a
20 desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives
to treat ophthalmic conditions has been the subject of
various patents, for example Ding et al U.S. Patent
5,474,979; Garst U.S. Patent 6,254,860; and Garst U.S.
25 6,350,442, this disclosure of each of which is incorporated
in its entirety herein by reference. In addition,
cyclosporin A compositions used in treating ophthalmic
conditions is the subject of a number of publications.
Such publications include, for example, "Blood
30 concentrations of cyclosporin a during long-term treatment
with cyclosporin a ophthalmic emulsions in patients with
moderate to severe dry eye disease," Small et al, *J Ocul*
Pharmacol Ther, 2002 Oct, 18(5):411-8; "Distribution of

cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999 Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; 10 "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group," Sall et al, 15 *Ophthalmology*, 2000 Apr, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) 20 regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the 25 ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1. 30

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2%

by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if
5 reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with
10 cyclosporin-containing emulsions.

Summary of the Invention

New methods of treating a human or animal using cyclosporin component-containing emulsions have been
15 discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for
20 reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug
25 interactions. The present methods can be easily practiced.

In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present
30 methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component

in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

5 It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present
10 compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more
15 quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced
20 amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of
25 advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is
30 relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome,

phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

5 Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable
10 concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

15 In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

20 Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

25 In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of
30 some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the

cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components,

polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and

every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

5 These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

Detailed Description

10 The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S.
15 pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is
20 less than 0.08.

 As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently
25 useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops
30 or similar form or other form so as to facilitate such topical administration.

 The present methods have been found to be very

effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with

reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, 5 thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin 10 component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the 15 human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations 20 below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. 25 After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3µm pore size C-8 reverse phase high pressure liquid chromatography 30 (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a

turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada).

Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed.

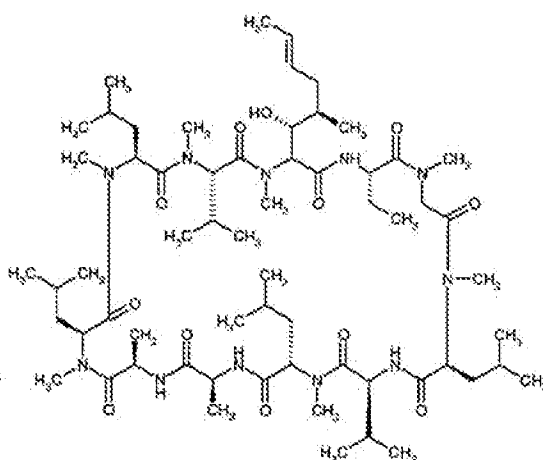
Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula I

5

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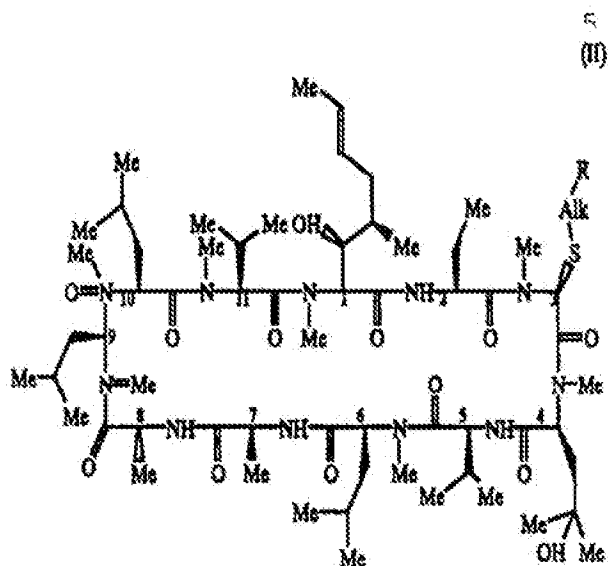
15

As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)³-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-

20 (Cyclo)alkylthio-Sar)³-(4'-hydroxy-MeLeu)⁴-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)³-cyclosporin A derivatives described below.

These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV)

30 respectively:

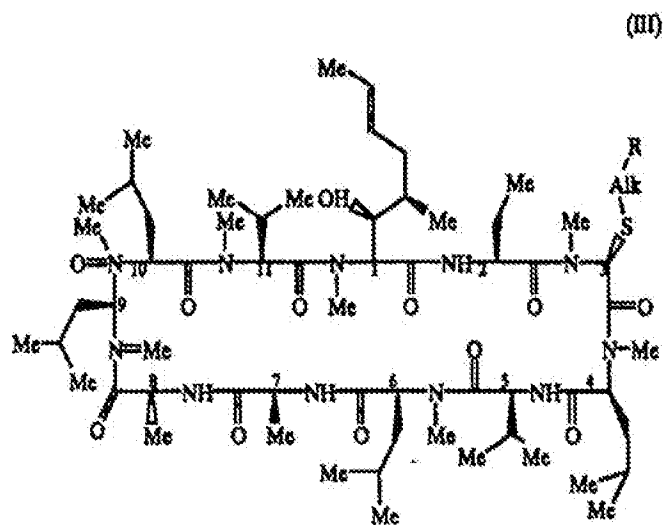
Formula II

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Formula III

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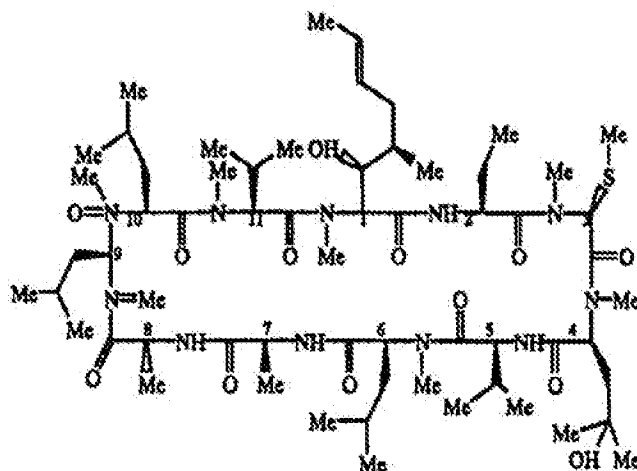
Formula IV

5

(f)

10

15



wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxy, carbonyl, $-NR_1R_2$ or $N(R_3)-(CH_2)_n-NR_1R_2$; wherein R_1, R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxy, carbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired

therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which

have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

5 Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof
10 are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high
15 concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

 The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion
20 compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

25 The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier
30 components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid

and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphoterteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers

of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

5 The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range
10 of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

 Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such
15 components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a
20 polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-
25 containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

 A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

30

metal carboxy methylcelluloses
metal carboxy methylhydroxyethylcelluloses

- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- 5 gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- peptides and polypeptides
- 10 alginic acid
- metal alginates
- homopolymers and copolymers of one or more of:
 - acrylic and methacrylic acids
 - metal acrylates and methacrylates
 - 15 vinylsulfonic acid
 - metal vinylsulfonate
 - amino acids, such as aspartic acid, glutamic acid and the like
 - metal salts of amino acids
 - 20 p-styrenesulfonic acid
 - metal p-styrenesulfonate
 - 2-methacryloyloxyethylsulfonic acids
 - metal 2-methacryloyloxethylsulfonates
 - 3-methacryloyloxy-2-hydroxypropylsulfonic acids
 - 25 metal 3-methacryloyloxy-2-
 - hydroxypropylsulfonates
 - 2-acrylamido-2-methylpropanesulfonic acids
 - metal 2-acrylamido-2-methylpropanesulfonates
 - allylsulfonic acid
 - 30 metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component

includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

10 The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the
15 presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the
20 polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in
25 accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful
30 tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range

of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates,

acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

5 The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like
10 and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application
15 involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

20 Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal
25 chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not
30 completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by

reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc.

5 An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial
10 peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and
15 other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include
20 viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like);
25 polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions.
30 The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the

total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in
5 producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily
10 phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid
15 oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase
20 is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant
25 components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is
30 allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion

concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter.

10 Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane

15 to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform

20 after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

25 The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room

30 temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
5		
10		
15		

20 These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to

Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be

understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. A composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin component to the hydrophobic component being less than 0.08.

22. The composition of claim 21 having a make-up so that when the composition is administered to an eye of a

human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin component.

23. The composition of claim 21 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

24. The composition of claim 21 wherein the cyclosporin component comprises cyclosporin A.

25. The composition of claim 21 in the form of an emulsion.

26. The composition of claim 21 wherein the hydrophobic component is present in an amount greater than 0.625% by weight of the composition.

27. The composition of claim 21 wherein the hydrophobic component is an oily material.

28. The composition of claim 21 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils, and mixtures thereof.

29. The composition of claim 21 wherein the hydrophobic component comprises castor oil.

30. The composition of claim 21 wherein the administering step comprises topically administering the composition to the eye of the human.

31. The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

METHODS OF PROVIDING THERAPEUTIC EFFECTS
USING CYCLOSPORIN COMPONENTS

Abstract of the Disclosure

5

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

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Application Number	unknown
Filing Date	herewith
First Named Inventor	Andrew Acheampong
Title	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
Art Unit	
Examiner Name	
Attorney Docket Number	17618CON7B (AP)

SIGNATURE of Applicant or Patent Practitioner

Signature	/Laura L. Wine/	Date	August 14, 2013
Name	Laura L. Wine	Telephone	714-246-6996
Registration Number	68,681		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications.

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City

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Email

I am the Applicant:

Inventor or Joint Inventor

Legal Representative of a Deceased or Legally Incapacitated Inventor

Assignee or Person to Whom the Inventor is Under an Obligation to Assign

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)

SIGNATURE of Applicant for Patent

Signature		Date	
Name	Debra D. Condino, Reg. No. 31,007	Telephone	714-246-2388
Title and Company	Assistant Secretary, Allergan, Inc.		

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. Submit multiple forms for more than one signature, see below *.

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I am the Applicant:

Inventor or Joint Inventor

Legal Representative of a Deceased or Legally Incapacitated Inventor

Assignee or Person to Whom the Inventor is Under an Obligation to Assign

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)

SIGNATURE of Applicant for Patent

Signature		Date	09/20/2012
Name	Debra D. Condino, Reg. No. 31,007	Telephone	714-246-2388
Title and Company	Assistant Secretary, Allergan, Inc.		

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. Submit multiple forms for more than one signature, see below *.

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VVAN11 ADJ #00000004 Mailroom Dt: 08/14/2013
 Seq No: 6005 Sales Acctg Dt: 08/15/2013 010885 13967168
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/967,168	Filing Date 08/14/2013	<input type="checkbox"/> To be Mailed
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ENTITY: LARGE SMALL MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE <small>(37 CFR 1.16(k), (l), or (m))</small>	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A	
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	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).			
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>				
<small>* If the difference in column 1 is less than zero, enter "0" in column 2.</small>			TOTAL	

APPLICATION AS AMENDED – PART II

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	08/14/2013	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total <small>(37 CFR 1.16(i))</small>	* 24	Minus	** 24	= 0	X \$80 = 0
	Independent <small>(37 CFR 1.16(h))</small>	* 3	Minus	***3	= 0	X \$420 = 0
	<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
					TOTAL ADD'L FEE	0

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=	X \$ =
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
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* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
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LDRC
/NICOLE NICHOLSON/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/967,168	Filing Date 08/14/2013	<input type="checkbox"/> To be Mailed
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ENTITY: LARGE SMALL MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE <small>(37 CFR 1.16(k), (l), or (m))</small>	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A	
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	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).			
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>				
* 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)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	
AMENDMENT	08/14/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR			
		* 24	Minus	** 24	= 0	X \$80 = 0	
		* 3	Minus	***3	= 0	X \$420 = 0	
		<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
		<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
					TOTAL ADD'L FEE	0	

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR			
		*	Minus	**	=	X \$ =	
		*	Minus	***	=	X \$ =	
		<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>					
		<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>					
					TOTAL ADD'L FEE		

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*

Examiner: TBA

Serial No.: 13/967,168

Group Art Unit: 1629

Filed: August 14, 2013

Confirmation No. 3265

For: METHODS OF PROVIDING
THERAPEUTIC EFFECTS USING
CYCLOSPORIN COMPONENTS

Customer No.: 51957

SUBMISSION OF SUBSTITUTE SPECIFICATION

Commissioner for Patents
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The Applicants file with this paper 1) a substitute specification, marked to show changes against the specification filed on August 14, 2013; and 2) a clean version of the specification, incorporating those changes. The applicants have revised the specification to show the changes made by the preliminary amendment filed on August 14, 2013; they have not added any new matter. Please replace the specification (excluding the claims) of the above-referenced application with the substitute specification.

As stated in the preliminary amendment filed on August 14, 2013, support for the amendment to the specification at page 4, line 25 – page 5, line 3 of the specification filed August 14, 2013, which correspond to page 3, line 26 – page 4, line 4 of the substitute and clean specifications filed herewith, may be found, at least, in U.S. Patent Nos. 5,474,979 and 6,254,860, which were previously incorporated by reference in the present application specification at page 1, lines 18-21. The amendment contains no new matter.

The Commissioner is hereby authorized to charge any fees required or necessary for the filing, processing or entering of this paper or any of the enclosed papers, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

/Laura L. Wine/

Laura L. Wine
Attorney of Record
Registration Number 68,681

Date: August 26, 2013

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

METHODS OF PROVIDING THERAPEUTIC EFFECTS
USING CYCLOSPORIN COMPONENTS

Related Application

5 This application is a continuation of copending U.S. Application Serial No. 13/961,835
filed August 7, 2013, which is a continuation of copending U.S. Application Serial No.
11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No.
10/927,857, filed August 27, 2004, now abandoned, which claimed the benefit of U.S.
Provisional Application No. 60/503,137 filed September 15, 2003, which are incorporated in
10 their entirety herein by reference.

Background of the Invention

 The present invention relates to methods of providing desired therapeutic effects to
humans or animals using compositions including cyclosporin components. More particularly,
15 the invention relates to methods including administering to an eye of a human or animal a
therapeutically effective amount of a cyclosporin component to provide a desired therapeutic
effect, preferably a desired ophthalmic or ocular therapeutic effect.

 The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions
has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S.
20 Patent 6,254,860; and Garst U.S. 6,350,442, this disclosure of each of which is incorporated in
its entirety herein by reference. In addition, cyclosporin A compositions used in treating
ophthalmic conditions is the subject of a number of publications. Such publications include, for
example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a
ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul*
25 *Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after
topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999
Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and
systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes,"
Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of
30 cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5;
"Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74;

and “Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group,” Sall et al, *Ophthalmology*, 2000 Apr, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have
5 been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for
10 Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations
15 less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or
20 ocular conditions with cyclosporin-containing emulsions.

Summary of the Invention

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing
25 desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or
30 drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as

increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can

increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea.

5 Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-
10 mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

15 Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid
20 residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

25 Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The
30 hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

5 Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

10 The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the
15 like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various
20 factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with
25 ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

30 The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

5 These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

Detailed Description

10 The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

15 As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

25 The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

30 The present methods are useful in treating any condition which is therapeutically

sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic
5 kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions
10 are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being
15 treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in
20 the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

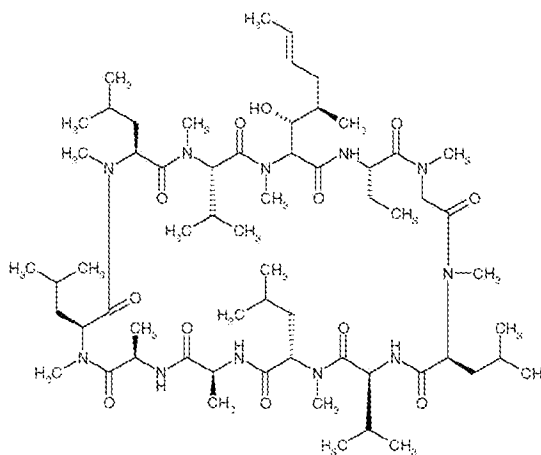
25 One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3 μ m pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are
30 gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction

monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula 1

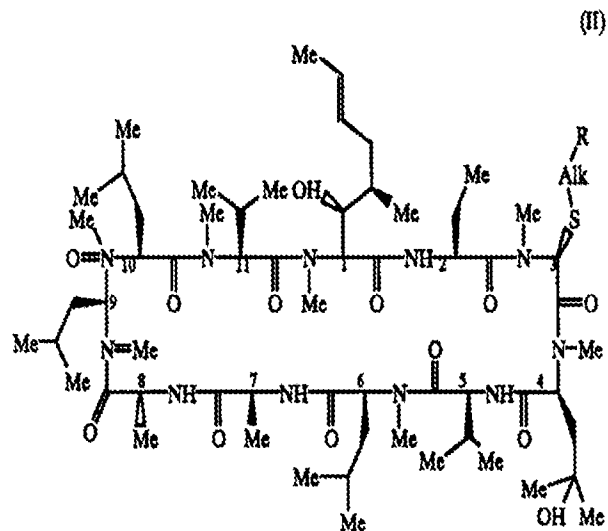


As used herein the term “derivatives” of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)³-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)³-(4'-hydroxy-MeLeu)⁴-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)³-cyclosporin A derivatives described below.

These cyclosporin derivatives are represented by the following general formulas (II),

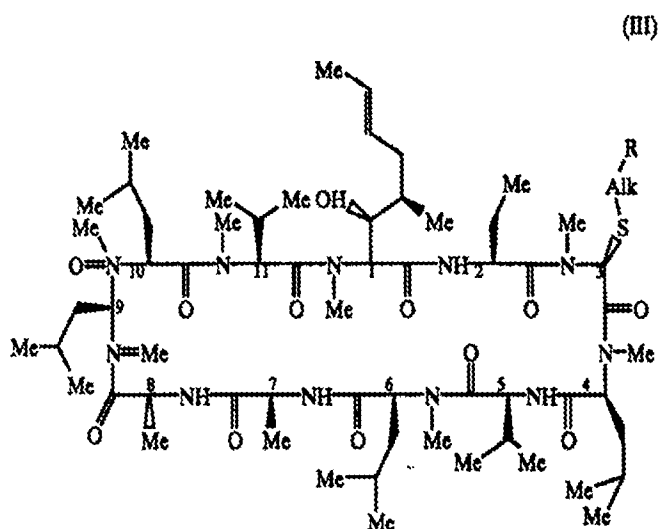
(III), and (IV) respectively:

Formula II



5

Formula III



10

Formula IV

considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

5 In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally
10 occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty
15 acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more
20 therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently
25 useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte
30 components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components,

preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained
5 in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

10 In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components
15 include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphoterteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include,
20 without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present
25 emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently
30 useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the

emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing
5 polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- 10 metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- 15 heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- 20 peptides and polypeptides
- alginate acid
- metal alginates
- homopolymers and copolymers of one or more of:
 - acrylic and methacrylic acids
 - 25 metal acrylates and methacrylates
 - vinylsulfonic acid
 - metal vinylsulfonate
 - amino acids, such as aspartic acid, glutamic acid and the like
 - metal salts of amino acids
 - 30 p-styrenesulfonic acid
 - metal p-styrenesulfonate

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2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulfonic acids
metal 3-methacryloyloxy-2-
5 hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

10

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials
15 include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the
20 presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02%
25 by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without
30 limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being

isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about

0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

5 In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by
10 routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

15 To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such
20 cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the
25 emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane
30 and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after

filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions.

5 The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

10 Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
Cyclosporin	0.1	0.05
15 Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
20 Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

25 These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to
 30 that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the

amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

5 Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

10 In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

15 Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

20 While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

METHODS OF PROVIDING THERAPEUTIC EFFECTS
USING CYCLOSPORIN COMPONENTS

Related Application

5 This application is a continuation of copending U.S. Application Serial No. 13/961,835
filed August 7, 2013, which is a continuation of copending U.S. Application Serial No.
11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No.
10/927,857, filed August 27, 2004, now abandoned, which claimed the benefit of U.S.
Provisional Application No. 60/503,137 filed September 15, 2003, which ~~is~~are incorporated in
10 ~~its~~their entirety herein by reference.

Background of the Invention

The present invention relates to methods of providing desired therapeutic effects to
humans or animals using compositions including cyclosporin components. More particularly,
15 the invention relates to methods including administering to an eye of a human or animal a
therapeutically effective amount of a cyclosporin component to provide a desired therapeutic
effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions
has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S.
20 Patent 6,254,860; and Garst U.S. 6,350,442, this disclosure of each of which is incorporated in
its entirety herein by reference. In addition, cyclosporin A compositions used in treating
ophthalmic conditions is the subject of a number of publications. Such publications include, for
example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a
ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul*
25 *Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after
topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999
Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and
systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes,"
Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of
30 cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5;
"Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74;

and “Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group,” Sall et al, *Ophthalmology*, 2000 Apr, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have
5 been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for
10 Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations
15 less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or
20 ocular conditions with cyclosporin-containing emulsions.

Summary of the Invention

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing
25 desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or
30 drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as

increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can

increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea.

5 Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-
10 mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

 In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

 Any suitable cyclosporin component effective in the present methods may be used.

 Cyclosporins are a group of nonpolar cyclic oligopeptides with known
15 immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

 In general, commercially available cyclosporins may contain a mixture of several
20 individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

 The term “cyclosporin component” as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

25 Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

 Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The
30 hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

5 Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

10 The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the
15 presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various
20 factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with
25 ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

30 The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

5 These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

Detailed Description

10 The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

15 As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the
20 composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the
25 blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye
30 irritation.

The present methods are useful in treating any condition which is therapeutically

sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic
5 kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions
10 are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being
15 treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in
20 the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

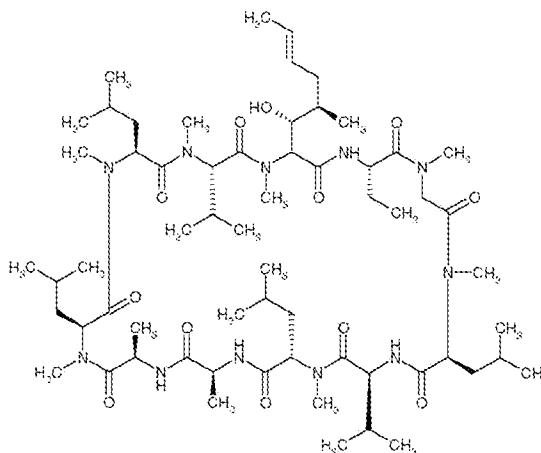
25 One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3 μ m pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are
30 gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction

monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

10 The chemical structure for cyclosporin A is represented by Formula 1

Formula 1

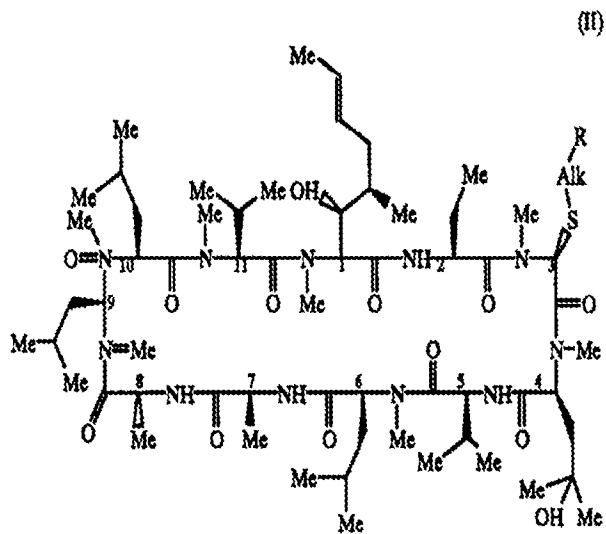


15 As used herein the term “derivatives” of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)³-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)³-(4'-hydroxy-MeLeu)⁴-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)³-cyclosporin A derivatives described below.

20 These cyclosporin derivatives are represented by the following general formulas (II),

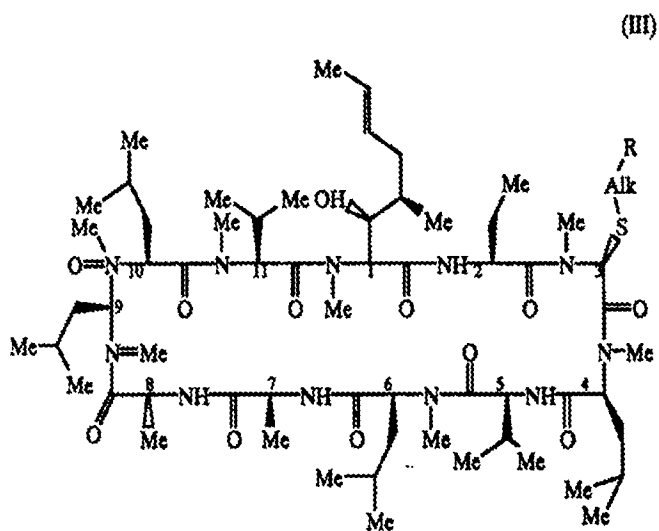
(III), and (IV) respectively:

Formula II



5

Formula III



10

Formula IV

considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

5 In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally
10 occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty
15 acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more
20 therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently
25 useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte
30 components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components,

preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphoteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the

emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- 10 metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- 15 heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- 20 peptides and polypeptides
- alginate acid
- metal alginates
- homopolymers and copolymers of one or more of:
 - acrylic and methacrylic acids
 - 25 metal acrylates and methacrylates
 - vinylsulfonic acid
 - metal vinylsulfonate
 - amino acids, such as aspartic acid, glutamic acid and the like
 - metal salts of amino acids
 - 30 p-styrenesulfonic acid
 - metal p-styrenesulfonate

2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulfonic acids
metal 3-methacryloyloxy-2-
5 hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

10

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials
15 include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the
20 presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02%
25 by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without
30 limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being

isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about

0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after

filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions.

5 The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

10 Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
Cyclosporin	0.1	0.05
15 Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
20 Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

25 These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to
30 that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the

amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

5 Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

10 In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

15 Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

20 While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

Electronic Acknowledgement Receipt

EFS ID:	16688455
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Bonnie Ferguson
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	26-AUG-2013
Filing Date:	
Time Stamp:	17:10:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	17618CON7BCoverSheet-forSubSpec.pdf	103470 41b6f01731473f120663aec362e0396b07a bdfff	no	2

Warnings:

Information:

2	Specification	17618CON7BNEWCLEANCOPY.pdf	484915	no	19
			c6286be433f08ace82415100c3453bb94c63331b		

Warnings:

Information:

3	Specification	17618CON7BNEWMARKEDUPS PEC.pdf	486916	no	19
			0718ec016d98e54ed197b3f4d925caad7de6bf1d		

Warnings:

Information:

Total Files Size (in bytes):			1075301		
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/967,168	08/14/2013	Andrew Acheampong	17618CON7B (AP)

CONFIRMATION NO. 3265

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

NOTICE



Date Mailed: 09/06/2013

INFORMATIONAL NOTICE TO APPLICANT

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

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

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Diane D. Tang-Liu
Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.



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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY,DOCKET.NO, TOT CLAIMS, IND CLAIMS. Row 1: 13/967,168, 08/14/2013, 1629, 2360, 17618CON7B (AP), 24, 3

CONFIRMATION NO. 3265

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

FILING RECEIPT



Date Mailed: 09/06/2013

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

Inventor(s)

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, NV;
James N. Chang, Newport Beach, CA;
David F. Power, Hubert, NC;

Applicant(s)

Allergan, Inc., Irvine, CA

Assignment For Published Patent Application

Allergan, Inc., Irvine, CA

Power of Attorney: The patent practitioners associated with Customer Number 51957

Domestic Priority data as claimed by applicant

This application is a CON of 13/961,835 08/07/2013
which is a CON of 11/897,177 08/28/2007
which is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

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 - A proper Authorization to Permit Access to Application by Participating Offices (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 09/03/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/967,168**

Projected Publication Date: 12/12/2013

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Preliminary Class

514

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

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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.

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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>.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/967,168	08/14/2013	Andrew Acheampong	17618CON7B (AP)

CONFIRMATION NO. 3265

POA ACCEPTANCE LETTER

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599



Date Mailed: 09/06/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/14/2013.

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.

/jchery/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13967168
	Filing Date		2013-08-14
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit		1629
	Examiner Name	TBD	
	Attorney Docket Number		17618-US-BCON7-AP

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
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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13967168
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First Named Inventor	ACHEAMPONG, ANDREW
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	17618-US-BCON7-AP

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**INFORMATION DISCLOSURE
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Art Unit		1629
Examiner Name	TBD	
Attorney Docket Number		17618-US-BCON7-AP

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Attorney Docket Number	17618-US-BCON7-AP

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70	U.S. Pending Application: 13/961,828 Filed on August 07, 2013	<input type="checkbox"/>
71	U.S. Pending Application: 13/916,835 Filed on August 07, 2013	<input type="checkbox"/>
72	U.S. Re-Examination Application: 90/009,944 Filed on August, 27, 2011	<input type="checkbox"/>

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13967168
Filing Date	2013-08-14
First Named Inventor	ACHEAMPONG, ANDREW
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	17618-US-BCON7-AP

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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*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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	13967168
	Filing Date	2013-08-14
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

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).

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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).

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- See attached certification statement.
- Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- None

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	/Laura L. Wine/	Date (YYYY-MM-DD)	2013-09-12
Name/Print	Laura L. Wine	Registration Number	68,681

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EFS ID:	16842741
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	12-SEP-2013
Filing Date:	14-AUG-2013
Time Stamp:	20:45:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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Electronic Acknowledgement Receipt

EFS ID:	16842791
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	12-SEP-2013
Filing Date:	14-AUG-2013
Time Stamp:	20:54:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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25	Non Patent Literature	90009944.pdf	1904560	no	39
			4b5aa1ab68a1940d5930d4265e9053cf672 03dc9		
Warnings:					
Information:					
Total Files Size (in bytes):			45812262		

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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.

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New International Application Filed with the USPTO as a Receiving Office

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ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE CA 92612-1599



Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/967,168
<p>1. THE REQUEST FILED <u>8/14/13</u> IS GRANTED.</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I). B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply; B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims,</u> or a multiple dependent claim; C. filing a <u>request for continued examination;</u> D. filing a notice of appeal; E. filing a request for suspension of action; F. mailing of a notice of allowance; G. mailing of a final Office action; H. completion of examination as defined in 37 CFR 41.102; or I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to Cheryl Gibson-Baylor at (571)272-3213, Office of Petitions. In his/her absence, calls may be directed to Brian W. Brown, (571)272-5338.</p> <p>Cheryl Gibson-Baylor <u>/Cheryl Gibson-Baylor/</u> [Signature]</p> <p>Petitions Paralegal Specialist (Title)</p>	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*

Serial No.: 13/967,168

Filed: August 14, 2013

For: METHODS OF PROVIDING
THERAPEUTIC EFFECTS USING
CYCLOSPORIN COMPONENTS

Examiner: Marcela M. Cordero Garcia

Group Art Unit: 1658

Confirmation No. 3265

Customer No.: 51957

COMMUNICATION UNDER MPEP 502.03

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

Dear Sir:

Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file.

Respectfully submitted,

/Laura L. Wine/

Date: October 1, 2013

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	17013229
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Alexis Swan
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	01-OCT-2013
Filing Date:	14-AUG-2013
Time Stamp:	19:19:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	17618CON7B-Comm-Under-502.pdf	104513 <small>a8e13eb8f5b365bd1f7f0093fd1d8940d0ea572b</small>	no	1

Warnings:

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Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce
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Electronic Petition Request	TERMINAL DISCLAIMER TO OBIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION
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Application Number	13967168
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Filing Date	14-Aug-2013
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First Named Inventor	Andrew Acheampong
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Attorney Docket Number	17618CON7B (AP)
------------------------	-----------------

Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
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<input checked="" type="checkbox"/> Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action <input checked="" type="checkbox"/> This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.
--

Owner	Percent Interest
Allergan, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

- 13967163 filed on 08/14/2013
- 13967179 filed on 08/14/2013
- 13967189 filed on 08/14/2013
- 13961835 filed on 08/07/2013
- 13961828 filed on 08/07/2013
- 13961818 filed on 08/07/2013
- 13961808 filed on 08/07/2013

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

- Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.
- I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

- Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).
- Applicant(s) status remains as SMALL ENTITY.
- Applicant(s) status remains as other than SMALL ENTITY.

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 United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

- An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 68681
- A sole inventor
- A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors
- A joint inventor; all of whom are signing this request
- The assignee of record of the entire interest that has properly made itself of record pursuant to 37 [CFR 3.71](#)

Signature	/Laura Wine/
Name	Laura Wine

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	13967168
Filing Date:	14-Aug-2013
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Lauren Barberena
Attorney Docket Number:	17618CON7B (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160

Pages:

Claims:

Miscellaneous-Filing:

Petition:

Patent-Appeals-and-Interference:

Post-Allowance-and-Post-Issuance:

Extension-of-Time:

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				160

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 13967168

Filing Date: 14-Aug-2013

Applicant/Patent under Reexamination: Acheampong et al.

Electronic Terminal Disclaimer filed on October 7, 2013

APPROVED

This patent is subject to a terminal disclaimer

DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	17062550
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Lauren Barberena
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	07-OCT-2013
Filing Date:	14-AUG-2013
Time Stamp:	19:54:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$160
RAM confirmation Number	6200
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	39375 233bd8d8bed5eb13a6c6de94d14e11bbf332a469	no	3

Warnings:**Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	30733 bfe0a1afc7538aac3480bde172c9685b9a31a278	no	2
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Warnings:**Information:**

Total Files Size (in bytes):	70108
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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.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
---------------------------	--

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 _____
filed on _____.

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.

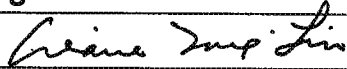
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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: Diane D. Tang-Liu Date (Optional) : _____

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 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.

Electronic Acknowledgement Receipt

EFS ID:	17068028
Application Number:	13967168
International Application Number:	
Confirmation Number:	3265
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Alexis Swan
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON7B (AP)
Receipt Date:	08-OCT-2013
Filing Date:	14-AUG-2013
Time Stamp:	13:42:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	17618-Tang-Liu-Declaration.pdf	115996 e6cccf12c8997e0c0437abbc948b1271c3c3b1e2	no	1

Warnings:

Information:

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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

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
Row 1: 13/967,168, 08/14/2013, Andrew Acheampong, 17618CON7B (AP), 3265
Row 2: 51957, 7590, 10/11/2013, ALLERGAN, INC., 2525 DUPONT DRIVE, T2-7H, IRVINE, CA 92612-1599
Row 3: EXAMINER, CORDERO GARCIA, MARCELA M
Row 4: ART UNIT, PAPER NUMBER, 1658
Row 5: NOTIFICATION DATE, DELIVERY MODE, 10/11/2013, 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):

patents_ip@allergan.com
pair_allergan@firsttofile.com

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

Status of the claims

2. Claims 37-60 are pending in the application. Claims 37-60 are presented for examination on the merits.

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.

3. Claim 37, 54 and 59 (and dependent claims thereof, i.e., 38-53, 55-60) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for containing the trademark/trade name Pemulen®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph (see MPEP 2173.05 (u)). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the