

22713 U.S. PTO

**UTILITY PATENT APPLICATION TRANSMITTAL***(Only for new nonprovisional applications under 37 CFR 1.53(b))*

Docket No: D-3111

Total Pages in this Submission

**TO THE U.S. PATENT AND TRADEMARK OFFICE**  
**PO BOX 1450**  
**ALEXANDRIA, VA 22313-1450**

19587 U.S. PTO  
 10/927857  
 082704

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 CFR 1.53(b) is a new utility patent application for an invention entitled:

**METHODS OF PROVIDING THERAPEUTIC EFFECTS  
 USING CYCLOSPORIN COMPONENTS**

and invented by:

**ACHEAMPONG ET AL**

If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:

Continuation  Divisional  Continuation-in-part (CIP) of prior application No.:

**Enclosed are Application Elements:**

- Filing Fee
- Specification having **34** page(s) and including the following:
- Title of the Invention
  - Cross References to Related Applications *(if applicable)*
  - Background of the Invention
  - Brief Summary of the Invention
  - Description of the Drawings
  - Detailed Description
  - Claim(s) as Classified Below
  - Abstract of the Disclosure
- \_ Sheets of Drawings(s) (37 CFR 113)  Formal  Informal
- Oath or Declaration  Executed  Unexecuted  
 Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
- Power of Attorney  Executed  Unexecuted  
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- Incorporation By Reference -- The entire disclosure of the prior application from which a copy of the oath or declaration is supplied under the above entry, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
- Computer Program in Microfiche *(Appendix)*

**Accompanying Application Parts**

- Assignment Papers (cover sheets & documents(s))  
 The prior application is assigned of record to  
 Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
- 37 CFR 3.73(B) Statement *(when there is an assignee)*
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- Information Disclosure Statement/PTO-1449
- Preliminary Amendment
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- APPLICATION DATA SHEET
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Copies of \_ IDS Cited Reference(s)

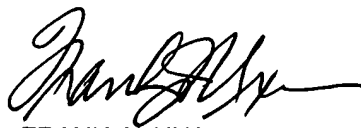
**Fee Calculation and Transmittal**

\* The filing fee is calculated on the basis of the claims existing in the prior application as amended by the accompanying preliminary amendment noted above.

CLAIMS AS FILED					
For	#Filed	#Allowed	#Extra	Rate	Fee
<b>Total Claims</b>	36	- 20 =	16	X \$18.00	\$288.00
<b>Independent Claims</b>	2	- 3 =		X \$86.00	\$ 0.00
<b>Multiple Dependent Claims</b> (check if applicable) <input type="checkbox"/>					\$ 0.00
<b>BASIC FEE</b>					\$ 770.00
<b>OTHER FEE</b> (specify purpose)				<b>ASSIGNMENT</b>	\$ 40.00
<small>(Applicant has small entity status under 37 CFR 1.9 and 1.27)</small>				<b>SMALL ENTITY STATUS</b>	--
<b>TOTAL FILING FEE</b>					\$1,098.00

- A check in the amount of \$ \_\_\_ to cover the filing fee and the assignment fee is enclosed.
- The Commissioner is hereby authorized to charge and/or credit Deposit Account Number 01-0885 as described below.
  - Charge the amount of \$1,098.00 as filing fee.
  - Credit any overpayment.
  - Charge any additional filing fees required under 37 CFR 1.16 and 1.17.

Respectfully Submitted,



FRANK J. UXA  
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D-3111

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**  
**PATENT**

In re application of:  
ACHEAMPONG ET AL. ) Group Art Unit: N/A  
)  
Serial No. N/A ) Examiner: N/A  
)  
Dated: Submitted herewith )  
)  
Title: METHODS OF PROVIDING )  
THERAPEUTIC EFFECTS USING )  
CYCLOSPORIN COMPONENTS )

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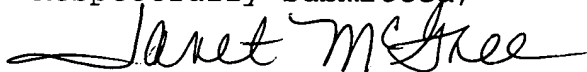
Date of Deposit: AUGUST 27, 2004

I hereby certify that the following documents as identified below are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

1. Application Transmittal
2. Application Data Sheet;
3. Application;
4. Declaration;
5. Assignment and Recordation Sheet; and
6. Return receipt postcard.

The 6 above-identified documents are enclosed herewith.

Respectfully submitted,



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SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

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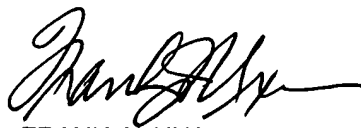
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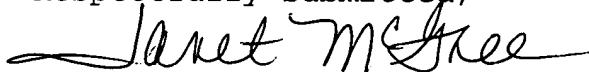
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**METHODS OF PROVIDING THERAPEUTIC EFFECTS**  
**USING CYCLOSPORIN COMPONENTS**

**Related Application**

5           This application claims the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which is incorporated in its entirety herein by reference.

**Background of the Invention**

10           The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a  
15           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  
20           various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S. 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  
25           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 Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after topical

30

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,  
lacrimial gland, and systemic blood following topical dosing  
5 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;  
"Cyclosporin & Emulsion & Eye," Stevenson et al,  
10 *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  
15 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  
ratio of cyclosporin A to castor oil in each of these  
25 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 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 cyclosporin-containing emulsions.

#### 10 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 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 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.

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 compositions, for example in treating dry eye disease, is  
10 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  
15 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  
20 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.

25 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  
30 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 concentration of the cyclosporin component. The  
10       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 some of the amino acids.

30       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. 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, 15 beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

20 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 25 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.

30 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 keratoconjunctivitis, 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, 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 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 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.

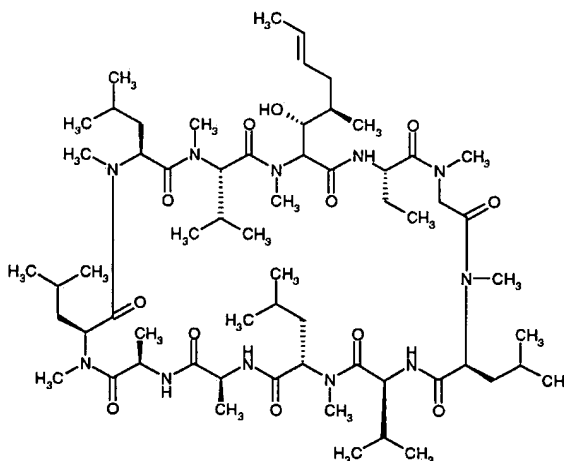
One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3 $\mu$ m pore size C-8 reverse phase high pressure liquid chromatography (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

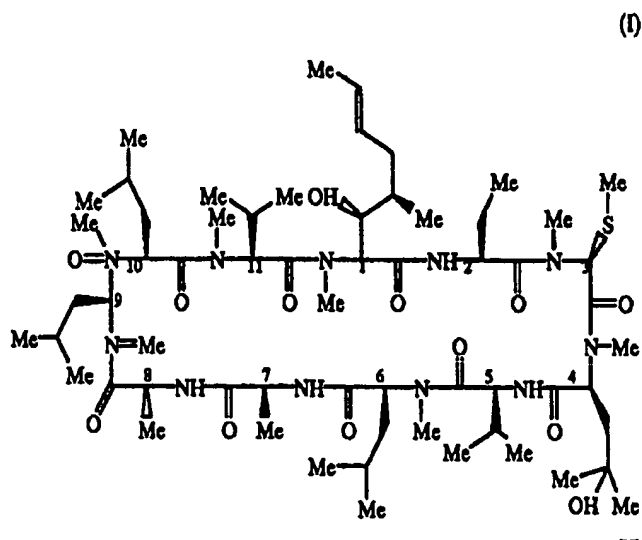
**Formula I**



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

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



Formula IV

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.

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 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 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 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 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  
5 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  
10 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  
15 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,  
20 without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphotheric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier  
25 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  
30 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 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.

10 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, 15 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.

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

metal carboxy methylcelluloses  
metal carboxy methylhydroxyethylcelluloses  
metal carboxy methylstarchs  
30 metal carboxy methylhydroxyethylstarchs  
hydrolyzed polyacrylamides and polyacrylonitriles

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

One particularly useful emulsion stabilizing component  
includes crosslinked polyacrylates, such as carbomers and  
30 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.

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 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% 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 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®.

5 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.

10 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.

25 30 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. 10 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. 20

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 25 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 30



emulsion may be already formed at this point.

5 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.

20 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 temperature.

25 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			
	Cyclosporin A	0.1	0.05
	Castor Oil	1.25	1.25
	Polysorbate 80	1.00	1.00
10	Premulen®	0.05	0.05
	Glycerine	2.20	2.20
	Sodium hydroxide	qs	qs
	Purified Water	qs	qs
	pH	7.2-7.6	7.2-7.6
15	Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

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

20 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  
 25 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  
 30 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  
10 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  
15 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  
20 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  
25 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  
30 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:

5 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.

DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS the specification of which

(check one) [X] is attached hereto [ ] was filed on as US Application Serial Number or PCT International Application Number and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56. I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. NONE

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Serial No. 60/503,137, September 15, 2003

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application. NONE

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 36,510, Stephen Donovan, Reg. No. 33,433, Brent A. Johnson, Reg. No. 51,851, Dean G. Stathakis, Reg. No. 54,465, Frank J. Uxa, Reg. No. 25,612, Donald E. Stout, Reg. No. 34,493, Robert D. Buyan, Reg. No. 32,460, Kenton R. Mullins, Reg. No. 36,331, Jo Anne M. Ybaben, Reg. No. 42,243, Linda Allyson Fox, Reg. No. 38,883, and Greg S. Hollrigel, Reg. No. 45,374.

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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.

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Continued...

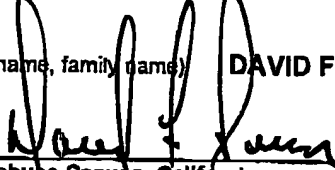
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## Application Information

Title Line One:: METHODS OF PROVIDING THERAPEUTIC  
Title Line Two:: EFFECTS USING CYCLOSPORIN COMPONENTS  
Total Drawing Sheets::  
Formal Drawings?::  
Application Type:: Utility

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Registration Number Seven::	Greg S. Holtrigel, Ph. D.....	45,374
Registration Number Eight::	Martin A. Voet.....	25,208
Registration Number Nine::	Robert J. Baran.....	25,806
Registration Number Ten::	Carlos A. Fisher.....	36,510
Registration Number Eleven::	Stephen Donovan.....	33,433
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**Continuity Information**

This application  
claims the benefit of::

>Application One:: 60/503,137  
Filing Date:: September 15, 2003

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**PATENT APPLICATION FEE DETERMINATION RECORD**

Effective October 1, 2003

Application or Docket Number

10927857

**CLAIMS AS FILED - PART I**

	(Column 1)	(Column 2)
TOTAL CLAIMS	36	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	36 minus 20=	* 16
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT <input type="checkbox"/>		

SMALL ENTITY TYPE

OR OTHER THAN SMALL ENTITY

RATE	FEE
BASIC FEE	385.00
XS 9=	
X43=	
+145=	
TOTAL	

RATE	FEE
BASIC FEE	770.00
XS18=	288
X86=	
+290=	
TOTAL	1058

\* If the difference in column 1 is less than zero, enter "0" in column 2

**CLAIMS AS AMENDED - PART II**

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total *	Minus **	=
	Independent *	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

SMALL ENTITY OR

OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE
XS 9=	
X43=	
+145=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
XS18=	
X86=	
+290=	
TOTAL ADDIT. FEE	

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total *	Minus **	=
	Independent *	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

RATE	ADDITIONAL FEE
XS 9=	
X43=	
+145=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
XS18=	
X86=	
+290=	
TOTAL ADDIT. FEE	

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total *	Minus **	=
	Independent *	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

RATE	ADDITIONAL FEE
XS 9=	
X43=	
+145=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
XS18=	
X86=	
+290=	
TOTAL ADDIT. FEE	

\* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.  
 \*\* If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."  
 \*\*\* If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."  
 The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.



PATENT APPLICATION SERIAL NO. \_\_\_\_\_

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE  
FEE RECORD SHEET

08/31/2004 EHAILE1 00000072 010885 10927857

01 FC:1001	770.00 DA
02 FC:1202	288.00 DA

PTO-1556  
(5/87)

D-3111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT

In re application of: Acheampong et al ) Group Art Unit: 1636  
Serial No. 10/927,857 ) Examiner: N/A  
Filed: August 27, 2004 )

For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper for Application Serial No. 10/927,857 is being facsimile transmitted to the Patent and Trademark Office fax number 703-872-9306 on the date shown below.

Janet McShee 11/12/04  
Signature Date

LETTER

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

Dear Sir:

Submitted herewith is a copy of the Power of Attorney filed in the above-identified application.

Pursuant to 37 CFR 1.32, indicated below is a list of the patent practitioners named in the Power of Attorney to be recognized by the Office as being of record in the application.

- Frank J. Uxa, Reg. No. 25,612
- Martin A. Voet, Reg. No. 25,208
- Robert J. Baran, Reg. No. 25,806
- Carlos Fisher, Reg. No. 36,510
- Stephen Donovan, Reg. No. 33,433
- Dean G. Stathakis, Reg. No. 54,465
- Brent A. Johnson, Reg. No. 51,851
- Linda A. Fox, Reg. No. 38,883
- Greg S. Hollrigel, Reg. No. 45,374

Respectfully submitted,

Frank J. Uxa  
Frank J. Uxa  
Attorney for Applicant

Reg. No. 25,612  
4 Venture, Suite 300  
Irvine, CA 92618  
(949) 450-1750  
Facsimile (714) 450-1764

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DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS the specification of which

(check one) [X] is attached hereto [ ] was filed on as US Application Serial Number or PCT International Application Number and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56. I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed. NONE

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Serial No. 60/503,137, September 15, 2003

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT international application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application. NONE

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office, connected therewith: Martin A. Voet, Reg. No. 25,208; Robert Baran, Reg. No. 25,806; Carlos A. Fisher, Reg. No. 38,510; Stephen Donovan, Reg. No. 33,433; Brent A. Johnson, Reg. No. 51,851; Dean G. Stathakis, Reg. No. 54,465; Frank J. Uxa, Reg. No. 26,612; Donald E. Stout, Reg. No. 34,493; Robert D. Buyan, Reg. No. 32,460; Kanton R. Mullins, Reg. No. 36,331; Jo Anne M. Ybaben, Reg. No. 42,243; Linda Aljyson Fox, Reg. No. 38,883; and Greg S. Helrigel, Reg. No. 45,374.

Address all telephone calls to Frank J. Uxa - Telephone: 949-450-1750
Address all correspondence to Frank J. Uxa
4 Venture, Suite 300
Irvine, CA 92618

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.

Full name of sole or first inventor (given name, family name) ANDREW ACHEAMPONG

Inventor's signature Residence Post Office Address Irvine, California 16 Wintergreen Irvine, CA 92604

Date 8/12/04
Citizenship USA

Full name of second inventor (given name, family name) DIANE TANG-LIU

Inventor's signature Residence Post Office Address Newport Beach, California 2515 Blackthorn Street Newport Beach, CA 92660

Date 8-12-2004
Citizenship USA

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NOV-12-04 03:30PM FROM-StoutUxaBuyanMullins

T-615 P.003/003 F-647

T-474 P.08/06 F-778

Aug-12-04 02:00 From-ALLERGAN LP<sup>LLC</sup> DEPARTMENT

+17142464248

Docket No. D-3111

Continued...

Full name of third inventor (given name, family name) **JAMES N. CHANG**

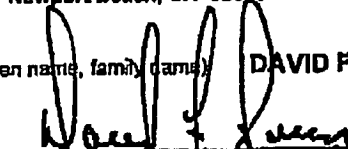
Inventor's signature  
Residence  
Post Office Address

  
Newport Beach, California  
36 Cervantes  
Newport Beach, CA 92660

Date 8/12/04  
Citizenship U.S.A.

Full name of fourth inventor (given name, family name) **DAVID F. POWER**

Inventor's signature  
Residence  
Post Office Address

  
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28335 Quiet Hill Lane  
Trabuco Canyon, CA 92679-1131

Date 8/12/04  
Citizenship U.S.A.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT

Continuation-in-part application of:  
ACHEAMPONG et al. ) Group Art Unit: 1636  
)  
Serial No. 10/927,857 ) Examiner: Unknown  
)  
Filed: August 27, 2004 )  
)  
For: METHODS OF PROVIDING )  
THERAPEUTIC EFFECTS USING )  
CYCLOSPORIN COMPONENTS )

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on or before

December 22, 2004  
Date  
Janet McGhee

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

INFORMATION DISCLOSURE STATEMENT

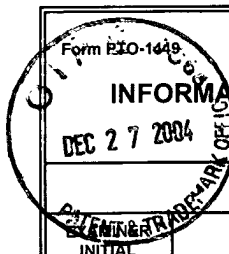
Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

Respectfully submitted,  
  
Frank J. Uxa  
Attorney for Applicant  
Reg. No. 25,612  
4 Venture, Suite 300  
Irvine, CA 92618  
(949) 450-1750  
Facsimile (949) 450-1764

FJUxa/ac

<p>Form PTO-1449</p> <p style="text-align: center;"><b>INFORMATION DISCLOSURE CITATION</b></p> <p style="text-align: center;"><b>IN AN APPLICATION</b></p> <p style="text-align: center;">(Use several sheets if necessary)</p>	Docket No.: D-3111	Application No.: 10/927,857
	Applicant: Acheampong et al.	
	Filing Date: August 27, 2004	Group Art Unit: 1636



**U. S. PATENT DOCUMENTS**

INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	3,278,447	10/1966	McNicholas			
	4,388,307	06/1983	Cavanak			
	4,649,047	03/1987	Kaswan			
	4,814,323	3/1989	Andrieu			
	4,839,342	06/1989	Kaswan			
	4,970,076	11/1990	Horrobin			
	4,990,337	02/1991	Kurihara et al.			
	4,996,193	02/1991	Hewitt et al.			
	5,286,730	02/1994	Caufield et al.			
	5,286,731	02/1994	Caufield et al.			
	5,342,625	08/1994	Hauer et al.			
	5,411,952	05/1995	Kaswan			

**FOREIGN PATENT DOCUMENTS**

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
					YES	NO

**OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)**

AA	Acheampong et al, "Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes," <i>Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York &amp; London, ©1998, pp. 1001-1004.</i>
AB	Acheampong et al, "Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs," <i>Curr Eye Res, Feb 1999, 18(2):91-103b.</i>
AC	Angelov et al, "Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion," <i>Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York &amp; London, ©1998, pp. 991-5.</i>
AD	Brewster et al, "Enhanced Delivery of Ganciclovir to the Brain through the Use of Redox Targeting," <i>Antimicrobial Agents and Chemotherapy, April 1994, 38(4):817-823.</i>
AE	Brewster et al, "Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl- $\beta$ -cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions," <i>J Pharm Sci, March 1997, 86(3):335-9.</i>

<b>EXAMINER</b>	<b>DATE CONSIDERED</b>
-----------------	------------------------

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



Form PTO-1449  <b>INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b> (Use several sheets if necessary)		Docket No.: D-3111		Application No.: 10/927,857			
		Applicant: Acheampong et al.					
		Filing Date: August 27, 2004		Group Art Unit: 1636			
<b>U. S. PATENT DOCUMENTS</b>							
EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE	
	5,474,979	12/1995	Ding et al.				
	5,504,068	04/1996	Komiya et al.				
	5,540,931	07/1996	Hewitt et al.				
	5,719,123	02/1998	Morley et al.				
	5,739,105	04/1998	Kim et al.				
	5,807,820	09/1998	Elias				
	5,843,452	12/1998	Wiedmann et al.				
	5,843,891	12/1998	Sherman				
	5,858,401	01/1999	Bhalani et al.				
	5,866,159	02/1999	Hauer et al.				
	5,891,846	04/1999	Ishida et al.				
	5,916,589	06/1999	Hauer et al.				
<b>FOREIGN PATENT DOCUMENTS</b>							
	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>							
	AA	Brewster et al, "Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl- $\beta$ -cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse," <i>J Pharm Sci</i> , October 1995, 84(10):1154-9.					
	AB	Sall et al, "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," <i>Ophthalmology</i> , April 2000, 107(4):631-9.					
	AC	Small et al, "Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A Ophthalmic Emulsions in Patients With Moderate to Severe Dry Eye Disease," <i>J Ocul Pharmacol Ther</i> , Oct 2002, 18(5):411-8.					
	AD	Stevenson et al., "Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry Eye Disease," <i>Ophthalmology</i> , May 2000, 107(5):967-74.					
	AE						
	AF						
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Form PTO-1449  <b>INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b> (Use several sheets if necessary)	Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.		
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**U. S. PATENT DOCUMENTS**

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,951,971	09/1999	Kawashima et al.			
	5,962,017	10/1999	Hauer et al.			
	5,981,479	11/1999	Ko et al.			
	5,981,607	11/1999	Ding et al.			
	5,998,365	12/1999	Sherman			
	6,008,191	12/1999	Singh et al.			
	6,008,192	12/1999	Al-Razzak et al.			
	6,022,852	02/2000	Klokkers et al.			
	6,024,978	02/2000	Hauer et al.			
	6,046,163	04/2000	Stuchlik et al.			
	6,159,933	12/2000	Sherman			
	6,254,860	07/2001	Garst			
	6,323,204	11/2001	Burke et al.			

**FOREIGN PATENT DOCUMENTS**

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION

**OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)**

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Form PTO-1449		Docket No.: D-3111		Application No.: 10/927,857			
<b>INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b> <small>(Use several sheets if necessary)</small>		Applicant: Acheampong et al.					
		Filing Date: August 27, 2004		Group Art Unit: 1636			
<b>U. S. PATENT DOCUMENTS</b>							
EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE	
	6,346,511	02/2002	Singh et al.				
	6,350,442	02/2002	Garst				
	6,413,547	07/2002	Bennett et al.				
	6,420,355	07/2002	Richter et al.				
	6,468,968	10/2002	Cavanak et al.				
	6,486,124	11/2002	Olbrich et al.				
	2001/0014665	08/2001	Fisher et al.				
	2003/0021816	01/2003	Kang et al.				
	2003/0044452	03/2003	Ueno				
	2003/0060402	03/2003	Cavanak et al.				
	2003/0087813	05/2003	Or et al				
	2003/0104992	06/2003	Or et al				
	2003/0109425	06/2003	Or et al				
	2003/0109426	06/2003	Or et al.				
	2003/0143250	07/2003	Hauer et al.				
<b>FOREIGN PATENT DOCUMENTS</b>							
	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>							
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D-3111

UNITED STATES PATENT AND TRADEMARK OFFICE

**PATENT**

In re application of:  
**ACHEAMPONG et al.** ) Group Art Unit: 1636  
) )  
Serial No. 10/927,857 ) Examiner: Unknown  
) )  
Filed: August 27, 2004 )  
) )  
For: METHODS OF PROVIDING )  
THERAPEUTIC EFFECTS USING )  
CYCLOSPORIN COMPONENTS )

I hereby certify that this correspondent is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on or before

March 22, 2005  
Date

Alicia Curran

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

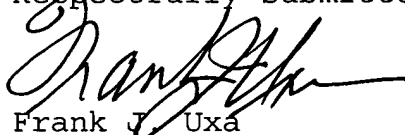
This SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed pursuant to 37 CFR 1.97(c) and is accompanied by a certification as specified in 37 CFR 1.97(e).

CERTIFICATION UNDER 37 CFR 1.97(e)

Each item of information contained in this Supplemental Information Disclosure Statement was cited in a communication

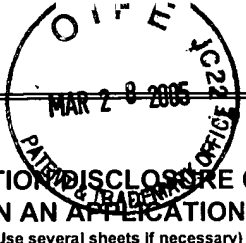
(the International Search Report) from a foreign patent office (The European Patent Office) acting as the International Search Authority in a counterpart foreign (PCT) patent application no more than three months prior to the filing of this Supplemental Information Disclosure Statement (a copy of the International Search Report is enclosed).

Respectfully submitted,



Frank J. Uxa  
Attorney for Applicant  
Reg. No. 25,612  
4 Venture, Suite 300  
Irvine, CA 92618  
(949) 450-1750  
Facsimile (949) 450-1764

FJUxa/ac



Form PTO-1449  <b>INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b> (Use several sheets if necessary)	Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.		
Filing Date: August 27, 2004		Group Art Unit: 1636

**U. S. PATENT DOCUMENTS**

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	2001/0036449 A1	11/2001	Garst			

**FOREIGN PATENT DOCUMENTS**

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
					YES	NO

**OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)**

AA	
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AC	
AD	
AE	
AF	
AG	
AH	

EXAMINER	DATE CONSIDERED
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10/927,857

FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 27 September 2006 (20060927/ED)

=> D QUE L14

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L2 ( 44)SEA FILE=BIOSIS ABB=ON PLU=ON ACHEAMPONG A?/AU  
L3 ( 117)SEA FILE=BIOSIS ABB=ON PLU=ON TANG LIU D?/AU  
L4 ( 4672)SEA FILE=BIOSIS ABB=ON PLU=ON CHANG J?/AU  
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L6 ( 213487)SEA FILE=BIOSIS ABB=ON PLU=ON EYE OR ASTHENOPIA OR CONJUNCTI  
VAL DISEASES OR CORNEAL DISEASES OR EYELID DISEASES OR  
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L7 ( 7948)SEA FILE=BIOSIS ABB=ON PLU=ON OCULAR HYPOTENSION OR OCULAR  
MOTILITY DISORDERS OR OPTIC NERVE DISEASES OR ORBITAL DISEASES  
OR PUPIL DISORDERS OR REFRACTIVE ERRORS OR RETINAL DISEASES  
OR SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR  
VITREORETINOPATHY OR VITREOUS DETACHMENT  
L8 ( 124285)SEA FILE=BIOSIS ABB=ON PLU=ON OIL  
L9 ( 23151)SEA FILE=BIOSIS ABB=ON PLU=ON EMULSI?  
L10 SEL PLU=ON L1 1- CHEM : 38 TERMS  
L11 ( 46884)SEA FILE=BIOSIS ABB=ON PLU=ON L10  
L12 ( 0)SEA FILE=BIOSIS ABB=ON PLU=ON ((L2 OR L3 OR L4 OR L5)) AND  
((L6 OR L7)) AND L8 AND L9 AND L11  
L13 ( 9)SEA FILE=BIOSIS ABB=ON PLU=ON ((L2 OR L3 OR L4 OR L5)) AND  
((L6 OR L7)) AND L11  
L14 9 SEA FILE=BIOSIS ABB=ON PLU=ON L12 OR L13

=> FILE EMBASE

FILE 'EMBASE' ENTERED AT 16:29:36 ON 02 OCT 2006  
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FILE COVERS 1974 TO 2 Oct 2006 (20061002/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default)  
and biweekly.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> D QUE L30

L15 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L16 ( 21)SEA FILE=EMBASE ABB=ON PLU=ON ACHEAMPONG A?/AU  
L17 ( 63)SEA FILE=EMBASE ABB=ON PLU=ON TANG LIU D?/AU  
L18 ( 3346)SEA FILE=EMBASE ABB=ON PLU=ON CHANG J?/AU  
L19 ( 272)SEA FILE=EMBASE ABB=ON PLU=ON POWER D?/AU  
L20 SEL PLU=ON L15 1- CHEM : 38 TERMS  
L21 ( 74476)SEA FILE=EMBASE ABB=ON PLU=ON L20

L22 ( 301867)SEA FILE=EMBASE ABB=ON PLU=ON EYE DISEASE+NT/CT  
L23 ( 8415)SEA FILE=EMBASE ABB=ON PLU=ON EMULSION+NT/CT  
L24 ( 5657)SEA FILE=EMBASE ABB=ON PLU=ON OIL/CT  
L25 ( 46238)SEA FILE=EMBASE ABB=ON PLU=ON D3.60.650./CT  
L26 ( 0)SEA FILE=EMBASE ABB=ON PLU=ON ((L16 OR L17 OR L18 OR L19))  
AND L21 AND L22 AND L23 AND ((L24 OR L25))  
L27 ( 2)SEA FILE=EMBASE ABB=ON PLU=ON ((L16 OR L17 OR L18 OR L19))  
AND L21 AND L22 AND L23  
L28 ( 5)SEA FILE=EMBASE ABB=ON PLU=ON ((L16 OR L17 OR L18 OR L19))  
AND L21 AND L22  
L29 ( 0)SEA FILE=EMBASE ABB=ON PLU=ON ((L16 OR L17 OR L18 OR L19))  
AND L21 AND L22 AND ((L24 OR L25))  
L30 5 SEA FILE=EMBASE ABB=ON PLU=ON L26 OR (L27 OR L28 OR L29)

=> FILE HCAPLUS

FILE 'HCAPLUS' ENTERED AT 16:29:47 ON 02 OCT 2006  
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FILE COVERS 1907 - 2 Oct 2006 VOL 145 ISS 15  
FILE LAST UPDATED: 1 Oct 2006 (20061001/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> D QUE L44

L31 ( 25)SEA FILE=HCAPLUS ABB=ON PLU=ON ACHEAMPONG A?/AU  
L32 ( 71)SEA FILE=HCAPLUS ABB=ON PLU=ON TANG LIU D?/AU  
L33 ( 7140)SEA FILE=HCAPLUS ABB=ON PLU=ON CHANG J?/AU  
L34 ( 227)SEA FILE=HCAPLUS ABB=ON PLU=ON POWER D?/AU  
L35 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L36 ( 36733)SEA FILE=HCAPLUS ABB=ON PLU=ON EYE, DISEASE+OLD,NT/CT  
L37 ( 24550)SEA FILE=HCAPLUS ABB=ON PLU=ON EMULSIFYING AGENTS/CT  
L38 ( 388102)SEA FILE=HCAPLUS ABB=ON PLU=ON OILS+OLD,NT/CT  
L39 SEL PLU=ON L35 1- CHEM : 38 TERMS  
L40 ( 23233)SEA FILE=HCAPLUS ABB=ON PLU=ON L39  
L41 ( 1)SEA FILE=HCAPLUS ABB=ON PLU=ON ((L31 OR L32 OR L33 OR L34))  
AND L40 AND L36 AND L37 AND L38  
L42 ( 29)SEA FILE=HCAPLUS ABB=ON PLU=ON ((L31 OR L32 OR L33 OR L34))  
AND L40  
L43 ( 4)SEA FILE=HCAPLUS ABB=ON PLU=ON L42 AND ((L36 OR L37 OR L38))  
L44 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L41 OR L43



=> FILE MEDLINE

FILE 'MEDLINE' ENTERED AT 16:30:01 ON 02 OCT 2006

FILE LAST UPDATED: 30 Sep 2006 (20060930/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).

See also:

<http://www.nlm.nih.gov/mesh/>

[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_med\\_data\\_changes.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html)

[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_2006\\_MeSH.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html)

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> D QUE L62

L45 ( 24)SEA FILE=MEDLINE ABB=ON PLU=ON ACHEAMPONG A?/AU  
L46 ( 63)SEA FILE=MEDLINE ABB=ON PLU=ON TANG LIU D?/AU  
L47 ( 3663)SEA FILE=MEDLINE ABB=ON PLU=ON CHANG J?/AU  
L48 ( 322)SEA FILE=MEDLINE ABB=ON PLU=ON POWER D?/AU  
L49 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L50 ( 9221)SEA FILE=MEDLINE ABB=ON PLU=ON EMULSIONS+NT/CT  
L51 ( 124)SEA FILE=MEDLINE ABB=ON PLU=ON EMULSIFYING AGENTS/CT  
L52 ( 34652)SEA FILE=MEDLINE ABB=ON PLU=ON OILS+NT/CT  
L53 ( 0)SEA FILE=MEDLINE ABB=ON PLU=ON L45 AND L46 AND L47 AND L48  
L54 SEL PLU=ON L49 1- CHEM : 38 TERMS  
L55 ( 39885)SEA FILE=MEDLINE ABB=ON PLU=ON L54  
L56 ( 320609)SEA FILE=MEDLINE ABB=ON PLU=ON EYE DISEASES+NT/CT  
L57 ( 0)SEA FILE=MEDLINE ABB=ON PLU=ON ((L45 OR L46 OR L47 OR L48))  
AND L56 AND L55 AND ((L50 OR L51)) AND L52  
L58 ( 2)SEA FILE=MEDLINE ABB=ON PLU=ON ((L45 OR L46 OR L47 OR L48))  
AND L56 AND L55 AND ((L50 OR L51))  
L59 ( 0)SEA FILE=MEDLINE ABB=ON PLU=ON ((L45 OR L46 OR L47 OR L48))  
AND L56 AND L55 AND L52  
L60 ( 5)SEA FILE=MEDLINE ABB=ON PLU=ON ((L45 OR L46 OR L47 OR L48))  
AND L56 AND L55  
L61 ( 5)SEA FILE=MEDLINE ABB=ON PLU=ON (L57 OR L58 OR L59 OR L60)  
L62 5 SEA FILE=MEDLINE ABB=ON PLU=ON L61 OR L53

=> FILE WPIX

FILE 'WPIX' ENTERED AT 16:30:10 ON 02 OCT 2006

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FILE LAST UPDATED: 2 OCT 2006 <20061002/UP>

MOST RECENT DERWENT UPDATE: 200663 <200663/DW>

DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:

[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://scientific.thomson.com/support/patents/coverage/latestupdates/>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE  
[http://www.stn-international.de/stndatabases/details/ipc\\_reform.html](http://www.stn-international.de/stndatabases/details/ipc_reform.html) and  
<http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf> <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS  
INDEX ENHANCEMENTS PLEASE VISIT:  
[http://www.stn-international.de/stndatabases/details/dwpi\\_r.html](http://www.stn-international.de/stndatabases/details/dwpi_r.html) <<<  
'BI,ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> D QUE L71

```
L63 (      1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L64 (      1)SEA FILE=WPIX ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L65 (      7)SEA FILE=WPIX ABB=ON  PLU=ON  TANG LIU D?/AU
L66 (    3666)SEA FILE=WPIX ABB=ON  PLU=ON  CHANG J?/AU
L67 (     57)SEA FILE=WPIX ABB=ON  PLU=ON  POWER D?/AU
L68 (      SEL  PLU=ON  L63 1- CHEM :      38 TERMS
L69 (    2231)SEA FILE=WPIX ABB=ON  PLU=ON  L68
L70 (     959)SEA FILE=WPIX ABB=ON  PLU=ON  RA0135/DCN OR 90981-1-0-0/DCRE
L71 (      6)SEA FILE=WPIX ABB=ON  PLU=ON  ((L64 OR L65 OR L66 OR L67)) AND
      ((L69 OR L70))
```

=> DUP REM L62 L14 L30 L71 L44  
FILE 'MEDLINE' ENTERED AT 16:31:07 ON 02 OCT 2006

FILE 'BIOSIS' ENTERED AT 16:31:07 ON 02 OCT 2006  
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FILE 'WPIX' ENTERED AT 16:31:07 ON 02 OCT 2006  
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PROCESSING COMPLETED FOR L62  
PROCESSING COMPLETED FOR L14  
PROCESSING COMPLETED FOR L30  
PROCESSING COMPLETED FOR L71  
PROCESSING COMPLETED FOR L44

```
L72      19 DUP REM L62 L14 L30 L71 L44 (10 DUPLICATES REMOVED)
      ANSWERS '1-5' FROM FILE MEDLINE
      ANSWERS '6-11' FROM FILE BIOSIS
      ANSWERS '12-13' FROM FILE EMBASE
      ANSWERS '14-19' FROM FILE WPIX
```

=> D IALL 1-5; D IALL 6-11; D IALL 12-13; D IALL ABEQ TECH 14-19

```
L72 ANSWER 1 OF 19      MEDLINE on STN      DUPLICATE 2
ACCESSION NUMBER:    2005132189      MEDLINE Full-text
DOCUMENT NUMBER:     PubMed ID: 15762768
TITLE:               Ocular pharmacokinetics and safety of ciclosporin
```

, a novel topical treatment for dry eye.  
AUTHOR: Tang-Liu Diane D-S; Acheampong Andrew  
CORPORATE SOURCE: Department of Pharmacokinetics and Drug Metabolism,  
Allergan Inc., Irvine, California 92612, USA..  
tang-liu\_diane@allergan.com  
SOURCE: Clinical pharmacokinetics, (2005) Vol. 44, No. 3, pp.  
247-61. Ref: 87  
Journal code: 7606849. ISSN: 0312-5963.  
PUB. COUNTRY: New Zealand  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200506  
ENTRY DATE: Entered STN: 15 Mar 2005  
Last Updated on STN: 28 Jun 2005  
Entered Medline: 27 Jun 2005

ABSTRACT:

**Ciclosporin** is a potent immunomodulator that acts selectively and locally when administered at the ocular surface. 0.05% **ciclosporin** ophthalmic emulsion has recently been approved by the US FDA for treatment of keratoconjunctivitis sicca (KCS) [dry-eye disease]. After topical application, **ciclosporin** accumulates at the ocular surface and cornea, achieving concentrations ( $\geq 0.236$  microg/g) that are sufficient for immunomodulation. Very little drug penetrates through the ocular surface to intraocular tissues. **Ciclosporin** is not metabolised in rabbit or dog eyes and may not be prone to metabolism in human eyes. Cultured human corneal endothelial and stromal cells exposed to **ciclosporin** in vitro exhibited no adverse effects and only minor effects on DNA synthesis. No ocular or systemic toxicity was seen with long-term ocular administration of **ciclosporin** at concentrations up to 0.4%, given as many as six times daily for 6 months in rabbits and 1 year in dogs. Systemic blood **ciclosporin** concentration after ocular administration was extremely low or undetectable in rabbits, dogs and humans, obviating concerns about systemic toxicity. In 12-week and 1-year clinical safety studies in dry-eye patients, the most common adverse event associated with the ophthalmic use of **ciclosporin** emulsion was ocular burning. No serious drug-related adverse events occurred. These data from in vitro, nonclinical and clinical studies indicate effective topical delivery of **ciclosporin** to desired target tissues along with a favourable safety profile, making 0.05% **ciclosporin** ophthalmic emulsion a promising treatment for KCS.

CONTROLLED TERM: Animals  
Chemistry, Physical  
Cyclosporine: AE, adverse effects  
\*Cyclosporine: PK, pharmacokinetics  
Cyclosporine: TU, therapeutic use  
\*Dry Eye Syndromes: DT, drug therapy  
\*Dry Eye Syndromes: ME, metabolism  
\*Eye: ME, metabolism  
Humans  
Immunosuppressive Agents: AE, adverse effects  
\*Immunosuppressive Agents: PK, pharmacokinetics  
Immunosuppressive Agents: TU, therapeutic use  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Immunosuppressive Agents)

L72 ANSWER 2 OF 19 MEDLINE on STN DUPLICATE 3  
ACCESSION NUMBER: 2002660073 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 12419092  
TITLE: Blood concentrations of **ciclosporin** a

during long-term treatment with **cyclosporin**  
a ophthalmic emulsions in patients with moderate to  
severe dry eye disease.

AUTHOR: Small David S; **Acheampong Andrew**; Reis Brenda;  
Stern Katherine; Stewart William; Berdy Gregg; Epstein  
Randy; Foerster Robert; Forstot Lance; **Tang-Liu Diane**  
D-S

CORPORATE SOURCE: Allergan, Inc Irvine, CA 92715, USA.  
SOURCE: Journal of ocular pharmacology and therapeutics : the  
official journal of the Association for Ocular Pharmacology  
and Therapeutics, (2002 Oct) Vol. 18, No. 5, pp. 411-8.  
Journal code: 9511091. ISSN: 1080-7683.

PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE III)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200212  
ENTRY DATE: Entered STN: 7 Nov 2002  
Last Updated on STN: 17 Dec 2002  
Entered Medline: 9 Dec 2002

ABSTRACT:

To quantify blood **cyclosporin A** (CsA) concentrations during  
treatment with CsA topical ophthalmic emulsions, blood was collected from 128  
patients enrolled in a Phase 3, multicenter, double-masked, randomized,  
parallel-group study of CsA eyedrops for treatment of moderate to severe dry  
eye disease. Patients received 0.05% CsA, 0.1% CsA, or vehicle b.i.d. for 6  
months; vehicle-treated patients then crossed over to 0.1% CsA b.i.d. for 6  
months. CsA concentrations were measured using a validated LC/MS-MS assay  
(quantitation limit = 0.1 ng/mL). No patient receiving 0.05% CsA had any  
quantifiable CsA in the blood (n = 96 samples). All but 7 of 128 (5.5%) trough  
blood samples from the 0.1% CsA group were below the quantitation limit for  
CsA; none exceeded 0.3 ng/mL. CsA was also below the limit of quantitation in  
205 of 208 (98.6%) of serial postdose blood samples collected from 26 patients  
during 1 dosing interval between months 9 and 12. The highest C(max) measured,  
0.105 ng/mL at 3 hours postdose, occurred in a 0.1% CsA-treated patient. These  
results indicate that long-term use of topical CsA ophthalmic emulsions at  
doses that are clinically efficacious for treating dry eye will not cause any  
system-wide effects.

CONTROLLED TERM: Check Tags: Female; Male  
Adult  
Aged  
Aged, 80 and over  
Anti-Inflammatory Agents, Non-Steroidal: AD,  
administration & dosage  
\*Anti-Inflammatory Agents, Non-Steroidal: BL, blood  
Anti-Inflammatory Agents, Non-Steroidal: TU, therapeutic  
use  
Area Under Curve  
Chromatography, High Pressure Liquid  
Cyclosporine: AD, administration & dosage  
\*Cyclosporine: BL, blood  
Cyclosporine: TU, therapeutic use  
Double-Blind Method  
Emulsions  
Humans  
Instillation, Drug

**Keratoconjunctivitis Sicca: BL, blood**  
**\*Keratoconjunctivitis Sicca: DT, drug therapy**

Middle Aged  
Ophthalmic Solutions

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Emulsions);  
0 (Ophthalmic Solutions)

L72 ANSWER 3 OF 19 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 1998348699 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9684074

TITLE: Topical **Cyclosporine A** in the management of postkeratoplasty glaucoma and corticosteroid-induced ocular hypertension (CIOH) and the penetration of topical 0.5% **cyclosporine A** into the cornea and anterior chamber.

AUTHOR: Perry H D; Donnenfeld E D; **Acheampong A**; Kanellopoulos A J; Sforza P D; D'Aversa G; Wallerstein A; Stern M

CORPORATE SOURCE: Department of Ophthalmology, North Shore University Hospital, Manhasset, New York 11030, USA.

SOURCE: The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc, (1998 Jul) Vol. 24, No. 3, pp. 159-65.

Journal code: 8302065. ISSN: 0733-8902.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199810

ENTRY DATE: Entered STN: 29 Oct 1998

Last Updated on STN: 29 Oct 1998

Entered Medline: 19 Oct 1998

ABSTRACT:

PURPOSE: To evaluate the effect on intraocular pressure (IOP) of substituting topical **Cyclosporine A** 0.5% for topical corticosteroids in patients with postkeratoplasty glaucoma and corticosteroid-induced ocular hypertension (CIOH). We also sought to determine the penetration of topical 0.5% **Cyclosporine A** into the cornea and anterior chamber.

METHODS: Topical **Cyclosporine A** 0.5% was prospectively substituted for topical corticosteroids in 47 patients (52 eyes) with postkeratoplasty glaucoma and CIOH in order to eliminate the IOP-elevating effect of topical corticosteroids, while maintaining protection against allograft rejection. Ten patients received 0.5% topical **Cyclosporine** before keratoplasty. Their corneal tissue and aqueous samples were evaluated by high pressure liquid chromatography for **Cyclosporine** levels.

RESULTS: Forty-eight of 52 eyes (92.3%) demonstrated a reduction of IOP at first followup (mean: -7.9 mmHg; range: -19 to +2). Mean followup was 10.3 months, ranging from 1 to 37 months. At last follow-up, mean IOP was -8.2 mm Hg. There were six allograft rejections, five of which were reversed with the reintroduction of topical corticosteroids. Graft clarity was maintained in 46 of 52 eyes (88%). The mean cornea **Cyclosporine** concentration was

3679 ng/gm (range: 1980 to 5520 ng/ gm) and aqueous humor mean concentration was 6.05 ng/mL (range: 0.4 to 15.5 ng/mL). CONCLUSIONS: Topical

\*\*\***Cyclosporine**\*\*\* **A** 0.5% may be substituted for topical corticosteroids to aid in the management of postkeratoplasty glaucoma and CIOH. However, the use of **Cyclosporine** in place of corticosteroids may be associated with an increased risk of immune rejections. The corneal penetration of topical **Cyclosporine** is excellent while the penetration into the anterior chamber is poor.

CONTROLLED TERM: Check Tags: Female; Male  
 Administration, Topical  
 Adolescent  
 Adult  
 Aged  
 Aged, 80 and over  
 Anterior Chamber: DE, drug effects  
 \*Anterior Chamber: ME, metabolism  
 Anterior Chamber: SU, surgery  
 Chromatography, High Pressure Liquid  
 Comparative Study  
 Cornea: DE, drug effects  
 Cornea: ME, metabolism  
 Cornea: SU, surgery  
 \*Cyclosporine: AD, administration & dosage  
 Cyclosporine: PK, pharmacokinetics  
 Follow-Up Studies  
 \*Glaucoma: DT, drug therapy  
 Glaucoma: ET, etiology  
 \*Glucocorticoids: AE, adverse effects  
 Humans  
 \*Immunosuppressive Agents: AD, administration & dosage  
 Immunosuppressive Agents: PK, pharmacokinetics  
 Intraocular Pressure: DE, drug effects  
 \*Keratoplasty, Penetrating: AE, adverse effects  
 Middle Aged  
 \*Ocular Hypertension: CI, chemically induced  
 Ocular Hypertension: DT, drug therapy  
 Ophthalmic Solutions  
 Prospective Studies

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
 CHEMICAL NAME: 0 (Glucocorticoids); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L72 ANSWER 4 OF 19 MEDLINE on STN  
 ACCESSION NUMBER: 1998298741 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 9635002  
 TITLE: **Cyclosporine** distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of **cyclosporine** to rabbit, dog, and human eyes.

AUTHOR: **Acheampong A**; Shackleton M; Lam S; Rudewicz P;  
**Tang-Liu D**

CORPORATE SOURCE: Allergan, Irvine, California, USA.  
 SOURCE: Advances in experimental medicine and biology, (1998) Vol. 438, pp. 1001-4.  
 Journal code: 0121103. ISSN: 0065-2598.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199809  
 ENTRY DATE: Entered STN: 25 Sep 1998  
 Last Updated on STN: 25 Sep 1998  
 Entered Medline: 15 Sep 1998

CONTROLLED TERM: Administration, Topical  
 Animals  
 \*Conjunctiva: ME, metabolism  
 \*Cornea: ME, metabolism  
 Cyclosporine: AD, administration & dosage

Cyclosporine: BL, blood  
\*Cyclosporine: PK, pharmacokinetics  
Dogs  
Dose-Response Relationship, Drug  
Humans  
Keratoconjunctivitis Sicca: DT, drug therapy  
\*Keratoconjunctivitis Sicca: ME, metabolism  
\*Lacrimal Apparatus: ME, metabolism  
Metabolic Clearance Rate  
Rabbits  
Tissue Distribution  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)

L72 ANSWER 5 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 1998298739 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 9635000  
TITLE: Preclinical safety studies of cyclosporine  
ophthalmic emulsion.  
AUTHOR: Angelov O; Wiese A; Yuan Y; Andersen J; Acheampong  
A; Brar B  
CORPORATE SOURCE: Allergan, Irvine, California, USA.  
SOURCE: Advances in experimental medicine and biology, (1998) Vol.  
438, pp. 991-5.  
Journal code: 0121103. ISSN: 0065-2598.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199809  
ENTRY DATE: Entered STN: 25 Sep 1998  
Last Updated on STN: 25 Sep 1998  
Entered Medline: 15 Sep 1998  
CONTROLLED TERM: Check Tags: Female; Male  
Animals  
Conjunctivitis: CI, chemically induced  
Cyclosporine: AD, administration & dosage  
\*Cyclosporine: TO, toxicity  
Dogs  
Emulsions  
Eye: CY, cytology  
\*Eye: DE, drug effects  
Eye: PA, pathology  
Rabbits  
Time Factors  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions)

L72 ANSWER 6 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
DUPLICATE 4  
ACCESSION NUMBER: 1998:276410 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199800276410  
TITLE: Effects of synthetic inhibitor of metalloproteinase and  
cyclosporin A on corneal haze after  
excimer laser photorefractive keratectomy in rabbits.  
AUTHOR(S): Chang, Jin Ho [Reprint author]; Kook, Myeong  
Cherl; Lee, Jin Hak; Chung, Hum; Wee, Won Ryang  
CORPORATE SOURCE: Dep. Ophthalmol., Seoul City Boramae Hosp., 395

SOURCE: Shindaebang-Dong, Tongjak-Gu, Seoul 1560-012, South Korea  
Experimental Eye Research, (April, 1998) Vol. 66, No. 4,  
pp. 389-396. print.  
CODEN: EXERA6. ISSN: 0014-4835.

DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 24 Jun 1998  
Last Updated on STN: 24 Jun 1998

ABSTRACT: To evaluate the effects of synthetic inhibitor of metalloproteinase (SIMP) and cyclosporin A (CsA) on corneal haze after excimer laser photorefractive keratectomy (PRK) in rabbits, PRK was performed on 60 rabbits. They were randomized to one of four groups: group A which received topical SIMP, group B which received topical CsA, group C which received both SIMP and CsA, and group D which received vehicles. Another 16 rabbits did not undergo PRK and were randomized to one of four groups: group E which received topical SIMP, group F which received topical CsA, group G which received both SIMP and CsA, and group H which received vehicles. SIMP solution (1 mM) was instilled every two hours and 2% cyclosporin was instilled four times a day, this was carried out for as long as 6 weeks after surgery. At one, two, four, and six weeks after surgery, slit lamp examination was performed with haze gradings recorded, and corneal specimens were obtained from groups A, B, C, and D. In groups E-H, all rabbits were killed after six weeks of eyedrops instillation. Light microscopy and immunohistochemistry for collagen types III, IV, and VI were performed on the specimens obtained. Slit lamp examination and light microscopy revealed that SIMP significantly reduced corneal haze after PRK, but CsA did not. Immunohistochemistry revealed that deposition of types III and IV collagen was detected in ablated area in groups A-D, and SIMP reduced the frequency of positive staining for type III collagen. In groups E-F, corneas were normal. These findings suggest that SIMP significantly reduced corneal haze and the synthesis of type III collagen after excimer laser PRK in rabbits.

CONCEPT CODE: Pharmacology - General 22002  
Sense organs - General and methods 20001

INDEX TERMS: Major Concepts  
Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Parts, Structures, & Systems of Organisms  
cornea: sensory system

INDEX TERMS: Diseases  
corneal haze: eye disease

INDEX TERMS: Chemicals & Biochemicals  
collagen: type III, type IV, type VI;  
cyclosporin A: topical administration;  
synthetic inhibitor of metalloproteinase [SIMP]: topical administration

INDEX TERMS: Methods & Equipment  
excimer laser photorefractive keratectomy: surgical method;  
immunohistochemistry: histochemical method;  
light microscopy: microscopy method; slit lamp examination: examination method

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rabbit  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 59865-13-3 (cyclosporin A)  
81669-70-7 (METALLOPROTEINASE)



L72 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
ACCESSION NUMBER: 2006:105948 BIOSIS Full-text  
DOCUMENT NUMBER: PREV200600105839

TITLE: Cytochrome P450 3A expression and activity in the rabbit  
lacrimal gland: Glucocorticoid modulation and the impact on  
androgen metabolism.

AUTHOR(S): Attar, Mayssa [Reprint Author]; Ling, Kah-Hiing John;  
**Tang-Liu, Diane D.-S.**; Neamati, Nouri; Lee, Vincent  
H. L.

CORPORATE SOURCE: Allergan Pharmaceut Inc, Dept Pharmacokinet and Drug Metab,  
Irvine, CA 92612 USA  
attar\_mayssa@allergan.com

SOURCE: IOVS, (DEC 2005) Vol. 46, No. 12, pp. 4697-4706.  
CODEN: IOVSDA. ISSN: 0146-0404.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 8 Feb 2006  
Last Updated on STN: 8 Feb 2006

ABSTRACT: PURPOSE. Cytochrome P450 3A (CYP3A) is an enzyme of paramount  
importance to drug metabolism. The expression and activity of CYP3A, an enzyme  
responsible for active androgen clearance, was investigated in the rabbit  
lacrimal gland. METHODS. Analysis of CYP3A expression and activity was  
performed on lacrimal gland tissues obtained from naive untreated and treated  
New Zealand White rabbits. For 5 days, treated rabbits received daily  
administration of vehicle or 0.1% or 1.0% dexamethasone, in the lower  
cul-de-sac of each eye. Changes in mRNA expression were monitored by  
real-time RT-PCR. Protein expression was confirmed by Western blot.  
Functional activity was measured by monitoring the metabolism of CYP3A probe  
substrates - namely, 7-benzyloxyquinoline (BQ) and [H-3] testosterone. RESULTS.  
Cytochrome P450 heme protein was detected at a concentration of 44.6  
picomoles/mg protein, along with its redox partner NADPH reductase and  
specifically CYP3A6 in the naive rabbit lacrimal gland. Genes encoding CYP3A6,  
in addition to the pregnane-X-receptor (PXR) and P-glycoprotein (P-gp) were  
expressed in the untreated tissue. BQ dealkylation was measured in the naive  
rabbit lacrimal gland at a rate of 14 +/- 7 picomoles/mg protein per minute.  
Changes in CYP3A6, P-gp, and androgen receptor mRNA expression levels were  
detected after dexamethasone treatment. In addition, dexamethasone treatment  
resulted in significant increases in BQ dealkylation and CYP3A6-mediated [H-3]  
testosterone metabolism. Concomitant increases in CYP3A6-mediated hydroxylated  
testosterone metabolites were observed in the treated rabbits. Furthermore,  
ketoconazole, all-trans retinoic acid, and cyclosporine inhibited  
CYP3A6 mediated [H-3] testosterone 6 beta hydroxylation in a  
concentration-dependent manner, with IC50 ranging from 3.73 to 435 mu  
M. CONCLUSIONS. The results demonstrate, for the first time, the expression and  
activity of CYP3A6 in the rabbit lacrimal gland. In addition, this pathway was  
shown to be subject to modulation by a commonly prescribed glucocorticoid and  
can be inhibited by known CYP3A inhibitors.

CONCEPT CODE: Biochemistry studies - General 10060  
Biochemistry studies - Nucleic acids, purines and  
pyrimidines 10062  
Biochemistry studies - Proteins, peptides and amino acids  
10064  
Biochemistry studies - Lipids 10066  
Biochemistry studies - Sterols and steroids 10067  
Biochemistry studies - Carbohydrates 10068  
Enzymes - General and comparative studies: coenzymes  
10802  
Pathology - Therapy 12512  
Metabolism - General metabolism and metabolic pathways

13002  
Endocrine - General 17002  
Sense organs - Physiology and biochemistry 20004  
Pharmacology - General 22002  
Pharmacology - Endocrine system 22016

INDEX TERMS: Major Concepts  
Pharmacology; Metabolism; Enzymology (Biochemistry and  
Molecular Biophysics); Endocrine System (Chemical  
Coordination and Homeostasis)

INDEX TERMS: Parts, Structures, & Systems of Organisms  
**eye:** sensory system; lacrimal gland: sensory  
system

INDEX TERMS: Chemicals & Biochemicals  
mRNA [messenger RNA]: expression; all-trans retinoic  
acid; glucocorticoids; androgen receptor; androgens;  
**cyclosporine**; P-glycoprotein [P-gp] [EC  
3.6.3.44]; heme protein; ketoconazole;  
pregnane-X-receptor; 7-benzyloxyquinoline; cytochrome  
P450 3A [CYP3A]: expression; tritiated testosterone;  
NADPH reductase; cytochrome P450 3A6; dexamethasone:  
glucocorticoid-drug, pharmacokinetics

INDEX TERMS: Methods & Equipment  
Western blot: electrophoretic techniques, immunologic  
techniques, laboratory techniques

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
New Zealand White rabbit (common)  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 302-79-4 (all-trans retinoic acid)  
63798-73-2 (**cyclosporine**)  
65277-42-1 (ketoconazole)  
131802-60-3 (7-benzyloxyquinoline)  
329322-82-9 (cytochrome P450 3A)  
329322-82-9 (CYP3A)  
9055-50-9 (NADPH reductase)  
359435-35-1 (cytochrome P450 3A6)  
50-02-2 (dexamethasone)

L72 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
ACCESSION NUMBER: 2000:236076 BIOSIS Full-text  
DOCUMENT NUMBER: PREV200000236076  
TITLE: Blood concentrations of **cyclosporin A**

(CsA) during twice-daily treatment of 0.05% and 0.1%  
**cyclosporine** ophthalmic emulsions in patients with  
moderate to severe keratoconjunctivitis sicca.  
AUTHOR(S): Small, D. S. [Reprint author]; **Acheampong, A.**  
[Reprint author]; Reis, B. [Reprint author]; Stewart, W.;  
Berdy, G.; Epstein, R.; Foerster, R.; Forstot, L.;  
**Tang-Liu, D.** [Reprint author]

CORPORATE SOURCE: Allergan Inc, Irvine, CA, USA  
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S69. print.  
Meeting Info.: Annual Meeting of the Association for  
Research in Vision and Ophthalmology. Fort Lauderdale,  
Florida, USA. April 30-May 05, 2000. Association for  
Research in Vision and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 7 Jun 2000  
Last Updated on STN: 5 Jan 2002

CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064  
Pathology - Therapy 12512  
Sense organs - Pathology 20006  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Clinical pharmacology 22005  
General biology - Symposia, transactions and proceedings 00520

INDEX TERMS: Major Concepts  
Ophthalmology (Human Medicine, Medical Sciences);  
Pharmacology

INDEX TERMS: Diseases  
keratoconjunctivitis sicca: **eye** disease,  
treatment  
Keratoconjunctivitis Sicca (MeSH)

INDEX TERMS: Chemicals & Biochemicals  
**cyclosporin A**: immunosuppressant-  
drug, blood concentrations, ophthalmic emulsions,  
twice-daily treatment

INDEX TERMS: Miscellaneous Descriptors  
Meeting Abstract

ORGANISM: Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human: patient  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates,  
Vertebrates

REGISTRY NUMBER: 59865-13-3 (cyclosporin A)

L72 ANSWER 9 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
ACCESSION NUMBER: 1997:540426 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199799839629  
TITLE: Preclinical safety of **cyclosporine** ophthalmic  
emulsion.

AUTHOR(S): Angelov, O.; Wiese, A.; Andersen, J.; Small, D.;  
**Acheampong, A.**; Yuan, Y.; Brar, B.

CORPORATE SOURCE: Allergan, Irvine, CA, USA  
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp.  
50.  
Meeting Info.: VIth International Symposium on Sjogren's  
Syndrome. Avon, Connecticut, USA. October 15-18, 1997.  
CODEN: JRHUA9. ISSN: 0315-162X.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Dec 1997  
Last Updated on STN: 12 Dec 1997.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520  
Biochemistry studies - General 10060  
Pathology - Therapy 12512  
Sense organs - General and methods 20001

Pharmacology - General 22002  
Routes of immunization, infection and therapy 22100

INDEX TERMS: Major Concepts  
Biochemistry and Molecular Biophysics; Pharmacology;  
Sense Organs (Sensory Reception)

INDEX TERMS: Chemicals & Biochemicals  
**CYCLOSPORINE**

INDEX TERMS: Miscellaneous Descriptors  
**CYCLOSPORINE; DRY EYES; OPHTHALMIC**  
**EMULSION; OPHTHALMIC-DRUG; PHARMACOKINETICS;**  
**PHARMACOLOGY; PRECLINICAL SAFETY; SENSE ORGANS; TOPICAL**  
**ADMINISTRATION**

ORGANISM: Classifier  
Canidae 85765  
Super Taxa  
Carnivora; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
dog  
Taxa Notes  
Animals, Carnivores, Chordates, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rabbit  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 59865-13-3Q (CYCLOSPORINE)  
63798-73-2Q (CYCLOSPORINE)

L72 ANSWER 10 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

ACCESSION NUMBER: 1997:540385 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199799839588  
TITLE: A dose-ranging clinical trial to assess the safety and  
efficacy of **cyclosporine** ophthalmic emulsion for  
the treatment of the ocular surface disease and  
inflammation associated with keratoconjunctivitis sicca  
(KCS).

AUTHOR(S): Donshik, P.; Reis, B. L.; Burk, C. T.; Stern, K. L.;  
**Acheampong, A.**

CORPORATE SOURCE: Allergan, Irvine, CA, USA  
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp.  
43.  
Meeting Info.: Vith International Symposium on Sjogren's  
Syndrome. Avon, Connecticut, USA. October 15-18, 1997.  
CODEN: JRHUA9. ISSN: 0315-162X.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Dec 1997  
Last Updated on STN: 12 Dec 1997

CONCEPT CODE: General biology - Symposia, transactions and proceedings  
00520  
Biochemistry studies - General 10060  
Pathology - Inflammation and inflammatory disease 12508  
Pathology - Therapy 12512

Sense organs - General and methods 20001  
Pharmacology - General 22002

INDEX TERMS: Major Concepts  
Biochemistry and Molecular Biophysics; Pathology;  
Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Chemicals & Biochemicals  
**CYCLOSPORINE**

INDEX TERMS: Miscellaneous Descriptors  
**CYCLOSPORINE; EFFICACY; EYE DISEASE;**  
KERATOCONJUNCTIVITIS SICCA; OCULAR INFLAMMATION; OCULAR  
SURFACE DISEASE; OPHTHALMIC EMULSION; OPHTHALMIC-DRUG;  
OPHTHALMOLOGY; PATIENT; PHARMACOLOGY; SAFETY

ORGANISM: Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates,  
Vertebrates

REGISTRY NUMBER: 59865-13-3Q (CYCLOSPORINE)  
63798-73-2Q (CYCLOSPORINE)

L72 ANSWER 11 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

ACCESSION NUMBER: 1996:206571 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199698762700  
TITLE: Ocular absorption of **cyclosporine** from an aqueous  
emulsion: Comparison to other eyedrop formulations.

AUTHOR(S): **Acheampong, A.; Tang-Liu, D.;**  
Shackleton, M.; Lam, S.; Angelov, O.; Ding, S.

CORPORATE SOURCE: Allergan Inc., Irvine, CA, USA  
SOURCE: Investigative Ophthalmology and Visual Science, (1996) Vol.  
37, No. 3, pp. S1026.  
Meeting Info.: 1996 Annual Meeting of the Association for  
Research in Vision and Ophthalmology. Fort Lauderdale,  
Florida, USA. April 21-26, 1996.  
CODEN: IOVSDA. ISSN: 0146-0404.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)

LANGUAGE: English  
ENTRY DATE: Entered STN: 2 May 1996  
Last Updated on STN: 2 May 1996

CONCEPT CODE: General biology - Symposia, transactions and proceedings  
00520  
Biochemistry studies - General 10060  
Pathology - Inflammation and inflammatory disease 12508  
Pathology - Therapy 12512  
Sense organs - General and methods 20001  
Sense organs - Physiology and biochemistry 20004  
Pharmacology - Drug metabolism and metabolic stimulators  
22003  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Sense organs, associated structures and  
functions 22031  
Routes of immunization, infection and therapy 22100  
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts

Immune System (Chemical Coordination and Homeostasis);  
Pathology; Pharmacology; Sense Organs (Sensory  
Reception)

INDEX TERMS: Chemicals & Biochemicals  
CYCLOSPORINE

INDEX TERMS: Miscellaneous Descriptors  
CYCLOSPORINE; DRUG DELIVERY SYSTEM;  
IMMUNOINFLAMMATORY EYE DISEASE;  
IMMUNOSUPPRESSANT-DRUG; MEETING ABSTRACT; MEETING  
POSTER; OPHTHALMIC-DRUG; PHARMACOKINETICS

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rabbit  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 59865-13-3Q (CYCLOSPORINE)  
63798-73-2Q (CYCLOSPORINE)

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ACCESSION NUMBER: 2005269839 EMBASE Full-text  
TITLE: Acute anterior uveitis and HLA-B27.  
AUTHOR: Chang J.H.; McCluskey P.J.; Wakefield D.  
CORPORATE SOURCE: Dr. D. Wakefield, School of Medical Sciences, University of  
New South Wales, Sydney, NSW 2052, Australia  
SOURCE: Survey of Ophthalmology, (2005) Vol. 50, No. 4, pp.  
364-388. .  
Refs: 236  
ISSN: 0039-6257 CODEN: SUOPAD  
PUBLISHER IDENT.: S 0039-6257(05)00041-X  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 012 Ophthalmology  
026 Immunology, Serology and Transplantation  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 18 Aug 2005  
Last Updated on STN: 18 Aug 2005

ABSTRACT: Acute anterior uveitis is the most common form of uveitis. HLA-B27-associated acute anterior uveitis is a distinct clinical entity that has wide-ranging medical significance due to its ocular, systemic, immunologic, and genetic features. The association between HLA-B27 and the spectrum of HLA-B27-associated inflammatory diseases remains one of the strongest HLA-disease associations known to date. This review examines acute anterior uveitis with particular focus on HLA-B27-associated acute anterior uveitis, including the epidemiology, immunopathology, association with HLA-B27 and its subtypes, clinical features, complications, prognosis, and potential new therapies such as anti-TNF $\alpha$  therapy and oral HLA-B27-peptide tolerance. There have been substantial recent advances in both clinical and basic scientific research in this field, including studies of the various animal

models of acute anterior uveitis and the HLA-B27 transgenic animals, and these are summarized in this review. To the ophthalmologist, HLA-B27-associated acute anterior uveitis is an important clinical entity that is common, afflicts relatively young patients in their most productive years, and is associated with significant ocular morbidity due to its typically recurrent attacks of inflammation and its potentially vision-threatening ocular complications. Furthermore, to the ophthalmologist and the internist, HLA-B27-associated acute anterior uveitis is also of systemic importance due to its significant association with extraocular inflammatory diseases. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

CONTROLLED TERM: Medical Descriptors:

- \*iridocyclitis: CO, complication
- \*iridocyclitis: DM, disease management
- \*iridocyclitis: DR, drug resistance
- \*iridocyclitis: DT, drug therapy
- \*iridocyclitis: EP, epidemiology
- \*iridocyclitis: ET, etiology
- \*iridocyclitis: PC, prevention
- \*iridocyclitis: SU, surgery

disease association

- systemic disease: CO, complication
- systemic disease: DT, drug therapy
- systemic disease: ET, etiology

immunological tolerance

- recurrent disease: CO, complication
- recurrent disease: DT, drug therapy
- recurrent disease: PC, prevention

- ankylosing spondylitis: DT, drug therapy
- ankylosing spondylitis: ET, etiology
- reactive arthritis: ET, etiology
- enteritis: DI, diagnosis
- enteritis: ET, etiology
- psoriatic arthritis: DT, drug therapy
- spondyloarthropathy: CO, complication
- spondyloarthropathy: ET, etiology
- juvenile rheumatoid arthritis: DT, drug therapy

sarcoidosis

- Behcet disease: DT, drug therapy**

mucocutaneous lymph node syndrome

**endophthalmitis**

Herpes simplex virus

Varicella zoster virus

Epstein Barr virus

Cytomegalovirus

Human immunodeficiency virus

Human T cell leukemia virus 1

- onchocerciasis: ET, etiology

Onchocerca volvulus

DNA polymorphism

- autoimmune disease: CO, complication
- autoimmune disease: DM, disease management
- autoimmune disease: DR, drug resistance
- autoimmune disease: DT, drug therapy
- autoimmune disease: EP, epidemiology
- autoimmune disease: ET, etiology
- autoimmune disease: PC, prevention
- autoimmune disease: SU, surgery

- chorioretinopathy: ET, etiology**
- Vogt Koyanagi syndrome: ET, etiology**

ocular histoplasmosis: ET, etiology  
 sympathetic ophthalmia: ET, etiology  
 interstitial nephritis: ET, etiology  
 Kirisawa uveitis: ET, etiology  
 intermediate uveitis: DT, drug therapy  
 intermediate uveitis: ET, etiology  
 rheumatic disease: DT, drug therapy  
 rheumatic disease: ET, etiology  
 sacroiliitis: CO, complication  
 sacroiliitis: DI, diagnosis  
 X ray film  
 eye synechia: CO, complication  
 cataract: CO, complication  
 intraocular hypertension: CO, complication  
 glaucoma: CO, complication  
 retina macula cystoid edema: DI, diagnosis  
 blindness: CO, complication  
 visual impairment: CO, complication  
 vitrectomy  
 fluorescence angiography  
 keratopathy: CO, complication  
 allergic encephalomyelitis  
 immunopathogenesis  
 heredity  
 major histocompatibility complex  
 chromosome  
 environmental factor  
 Chlamydia trachomatis  
 Klebsiella pneumoniae  
 Salmonella enteritidis  
 Salmonella typhimurium  
 Yersinia enterocolitica  
 Shigella  
 Campylobacter jejuni  
 Gram negative infection: DT, drug therapy  
 Gram negative infection: ET, etiology  
 colonoscopy  
 enterocolitis: ET, etiology  
 enthesitis: ET, etiology  
 psoriasis: ET, etiology  
 male genital tract inflammation: ET, etiology  
 keratitis: ET, etiology  
 hyperkeratosis: ET, etiology  
 uveoretinitis  
 molecular mimicry  
 antigen presenting cell  
 immunomodulation  
 Crohn disease: DT, drug therapy  
 uveitis: CO, complication  
 uveitis: DM, disease management  
 uveitis: DR, drug resistance  
 uveitis: DT, drug therapy  
 uveitis: EP, epidemiology  
 uveitis: ET, etiology  
 uveitis: PC, prevention  
 uveitis: SU, surgery  
 idiopathic disease: DT, drug therapy  
 scleritis: DT, drug therapy  
 multiple sclerosis: DT, drug therapy  
 rheumatoid arthritis: DT, drug therapy



drug cost  
side effect: SI, side effect  
drug safety  
human  
nonhuman  
clinical trial  
review  
priority journal

CONTROLLED TERM:

Drug Descriptors:  
tumor necrosis factor alpha antibody: CT, clinical trial  
tumor necrosis factor alpha antibody: DT, drug therapy  
tumor necrosis factor alpha antibody: IV, intravenous drug administration  
tumor necrosis factor alpha antibody: PD, pharmacology  
tumor necrosis factor alpha antibody: SC, subcutaneous drug administration  
HLA B27 antigen: CT, clinical trial  
HLA B27 antigen: DT, drug therapy  
HLA B27 antigen: PO, oral drug administration  
HLA antigen class 1: EC, endogenous compound  
HLA antigen class 2: EC, endogenous compound  
immunosuppressive agent: DT, drug therapy  
corticosteroid: DT, drug therapy  
corticosteroid: IO, intraocular drug administration  
corticosteroid: VI, intravitreal drug administration  
corticosteroid: TP, topical drug administration  
endotoxin  
bacterium lipopolysaccharide  
melanin  
**cyclosporin**  
myelin basic protein  
cytokine: EC, endogenous compound  
HLA DR4 antigen: EC, endogenous compound  
transporter associated with antigen processing 1: EC, endogenous compound  
epitope: EC, endogenous compound  
cycloplegic agent: DT, drug therapy  
cycloplegic agent: TP, topical drug administration  
infliximab: CT, clinical trial  
infliximab: DT, drug therapy  
infliximab: IV, intravenous drug administration  
infliximab: PD, pharmacology  
etanercept: CT, clinical trial  
etanercept: DT, drug therapy  
etanercept: PD, pharmacology  
etanercept: SC, subcutaneous drug administration  
methotrexate  
myelin: CT, clinical trial  
myelin: DT, drug therapy  
myelin: PO, oral drug administration  
collagen: CT, clinical trial  
collagen: DT, drug therapy  
collagen: PO, oral drug administration  
uveitogenic peptide: CT, clinical trial  
uveitogenic peptide: DT, drug therapy  
uveitogenic peptide: PO, oral drug administration  
peptide derivative: CT, clinical trial  
peptide derivative: DT, drug therapy  
peptide derivative: PO, oral drug administration  
antibiotic agent: DT, drug therapy

salazosulfapyridine: DT, drug therapy  
ciprofloxacin: AE, adverse drug reaction  
ciprofloxacin: CT, clinical trial  
ciprofloxacin: DT, drug therapy  
ciprofloxacin: PE, pharmacoconomics  
unclassified drug

CAS REGISTRY NO.: (melanin) 8049-97-6; (cyclosporin) 79217-60-0;  
(infliximab) 170277-31-3; (etanercept) 185243-69-0,  
200013-86-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5;  
(collagen) 9007-34-5; (salazosulfapyridine) 599-79-1;  
(ciprofloxacin) 85721-33-1

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ACCESSION NUMBER: 2001289213 EMBASE Full-text  
TITLE: Corneal neovascularization.  
AUTHOR: Chang J.-H.; Gabison E.E.; Kato T.; Azar D.T.  
CORPORATE SOURCE: Dr. D.T. Azar, Massachusetts Eye and Ear Infirmary, 243  
Charles Street, Boston, MA 02114, United States.  
dazar@meei.harvard.edu  
SOURCE: Current Opinion in Ophthalmology, (2001) Vol. 12, No. 4,  
pp. 242-249. .  
Refs: 102  
ISSN: 1040-8738 CODEN: COOTEF  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 012 Ophthalmology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 30 Aug 2001  
Last Updated on STN: 30 Aug 2001

ABSTRACT: Corneal neovascularization (NV) is a sight-threatening condition usually associated with inflammatory or infectious disorders of the ocular surface. It has been shown in the field of cancer angiogenesis research that a balance exists between angiogenic factors (such as fibroblast growth factor and vascular endothelial growth factor) and anti-angiogenic molecules (such as angiostatin, endostatin, or pigment epithelium derived factor) in the cornea. Several inflammatory, infectious, degenerative, and traumatic disorders are associated with corneal NV, in which the balance is tilted towards angiogenesis. The pathogenesis of corneal NV may be influenced by matrix metalloproteinases and other proteolytic enzymes. New medical and surgical treatments, including angiostaticsteroids, nonsteroidal inflammatory agents, argon laser photocoagulation, and photodynamic therapy have been effective in animal models to inhibit corneal NV and transiently restore corneal "angiogenic privilege." .COPYRGT. 2001 Lippincott Williams & Wilkins, Inc.

CONTROLLED TERM: Medical Descriptors:  
\*cornea neovascularization: DT, drug therapy  
\*cornea neovascularization: ET, etiology  
\*cornea neovascularization: SU, surgery  
visual impairment  
eye inflammation  
eye infection  
disease association  
eye injury  
degeneration  
pathogenesis  
protein degradation  
argon plasma coagulation

photodynamic therapy  
 transplantation  
 human  
 nonhuman  
 animal experiment  
 animal model  
 review  
 priority journal  
 Drug Descriptors:  
 angiogenic factor  
 fibroblast growth factor  
 vasculotropin  
 angiogenesis inhibitor  
 angiostatin  
 endostatin  
 pigment epithelium derived factor  
 matrix metalloproteinase  
 proteinase  
 steroid: DT, drug therapy  
 nonsteroid antiinflammatory agent: DT, drug therapy  
 calcitriol: DT, drug therapy  
 thrombocyte activating factor antagonist: DT, drug therapy  
**cyclosporin A: DT, drug therapy**  
 tsukubaenolide: DT, drug therapy  
 thalidomide: DT, drug therapy  
 prolactin: DT, drug therapy  
 curcumin: DT, drug therapy  
 protein farnesyltransferase inhibitor: DT, drug therapy  
 methotrexate: DT, drug therapy  
 indometacin: DT, drug therapy  
 prostaglandin synthase inhibitor: DT, drug therapy  
 (fibroblast growth factor) 62031-54-3; (vasculotropin)  
 127464-60-2; (angiostatin) 172642-30-7, 86090-08-6;  
 (endostatin) 187888-07-9; (pigment epithelium derived  
 factor) 197980-93-1; (proteinase) 9001-92-7; (calcitriol)  
 32222-06-3, 32511-63-0, 66772-14-3; (**cyclosporin**  
**A) 59865-13-3, 63798-73-2;**  
 (tsukubaenolide) 104987-11-3; (thalidomide) 50-35-1;  
 (prolactin) 12585-34-1, 50647-00-2, 9002-62-4; (curcumin)  
 458-37-7; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5;  
 (indometacin) 53-86-1, 74252-25-8, 7681-54-1

CAS REGISTRY NO.:

L72 ANSWER 14 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 1  
 ACCESSION NUMBER: 2005-232171 [24] WPIX  
 DOC. NO. CPI: C2005-073704  
 TITLE: Use of emulsions containing water, hydrophobic component,  
 and reduced concentration of **cyclosporin**  
 component for treating ophthalmic conditions e.g. dry eye  
 syndrome.  
 DERWENT CLASS: B03 B04  
 INVENTOR(S): **ACHEAMPONG, A; CHANG, J N;**  
**POWER, D F; TANG-LIU, D**  
 PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC  
 COUNTRY COUNT: 108  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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 US 2005059583 A1 20050317 (200524)\* 10 A61K038-13  
 WO 2005032577 A1 20050414 (200526) EN A61K038-13  
 RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE  
 LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE  
 DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG  
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ  
 OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG  
 US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005059583	A1 Provisional	US 2003-503137P	20030915
		US 2004-927857	20040827
WO 2005032577	A1	WO 2004-US29067	20040907

PRIORITY APPLN. INFO: US 2003-503137P 20030915; US  
 2004-927857 20040827

INT. PATENT CLASSIF.:

MAIN: A61K038-13  
 SECONDARY: A61K047-44; A61P027-02

BASIC ABSTRACT:

US2005059583 A UPAB: 20050414

NOVELTY - Treatment of ophthalmic conditions involves administration of a composition in the form of an emulsion comprising water, a **cyclosporin** component (less than 0.1 weight%) and a hydrophobic component. A weight ratio of the **cyclosporin** component to the hydrophobic component is less than 0.08.

ACTIVITY - Ophthalmological; Immunosuppressive; Antiinflammatory.

Test details are described but no results are given.

MECHANISM OF ACTION - None given.

USE - For treating ophthalmic conditions including dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, and corneal graft rejection (claimed).

ADVANTAGE - The method improves therapeutic efficacy of **cyclosporin**; reduces risks of side effects and/or drug interactions by reducing the drug concentration such that the blood of the human or animal has at most 0.1 ng/ml or no detectable concentration of the **cyclosporin** component; enhances patient safety; and provides increased flexibility to physicians for prescribing such an easily administrable composition. The emulsion is thermodynamically stable and exhibits a shelf life of greater than a year at room temperature. The relatively high concentration of hydrophobic component provides for a more rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion caused by the presence of the emulsion in the eye. Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B02-C; B04-A10; B04-B01C1; B12-M03; B14-G02C;  
 B14-N03

TECH UPTX: 20050414

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition comprises greater than 0.625 wt.% of the hydrophobic component, and additionally an emulsifier component, tonicity (preferably organic tonicity) component, and a polyelectrolyte component for stabilizing the composition. The composition has a pH of 7 - 8 (preferably 7.2 - 7.6).

Preferred Components: The **cyclosporin** component is **cyclosporin A** and/or its derivatives; and is solubilized in the

hydrophobic component. The hydrophobic component is an oily material selected from vegetable oil, animal oil, mineral oil and/or synthetic oil (preferably castor oil).

Preferred Method: 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. The blood of the human or animal has a concentration of the cyclosporin component of at most 0.1 ng/ml.

L72 ANSWER 15 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2006-253421 [26] WPIX  
 DOC. NO. CPI: C2006-082531  
 TITLE: Biodegradable lacrimal canalicular insert for treating ophthalmic conditions e.g. dry eye comprises biodegradable polymer and therapeutic component in member structured to be placed in lacrimal canaliculus.  
 DERWENT CLASS: A96 B05 B07 D22  
 INVENTOR(S): CHANG, C; CHANG, J; JORDAN, R S; SCHIFFMAN, R  
 PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC  
 COUNTRY COUNT: 111  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2006031658	A2	20060323	(200626)*	EN	27	A61K009-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006031658	A2	WO 2005-US32222	20050907

PRIORITY APPLN. INFO: US 2004-608628P 20040910  
 INT. PATENT CLASSIF.:

MAIN: A61K009-00

BASIC ABSTRACT:

WO2006031658 A UPAB: 20060421

NOVELTY - A biodegradable lacrimal canalicular insert (D1) comprises a biodegradable polymer component (P1) and a therapeutic component (P2) in a member structured to be placed in a lacrimal canaliculus of an individual and to release (P2) to provide a benefit to the individual.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for producing (D1) involving: forming at least one (P1) and at least one (P2) into a member structured to be placed in a lacrimal canaliculus of an individual.

ACTIVITY - Ophthalmological; Antiinflammatory; Antidiabetic; Vasotropic; Antitubercular; Tuberculostatic; Vulnerary; Cytostatic; Antibacterial; Osteopathic.

MECHANISM OF ACTION - None given.

USE - As biodegradable lacrimal canalicular insert placed into a lacrimal canaliculus of an individual e.g. human or animal to treat conditions of at least one of eye, a nasolacrimal system, and a nose of the human or animal; in

the treatment of ophthalmic conditions (claimed) such as dry eye and ocular conditions such as anterior segment disease, anterior uveitis, conjunctivitis, glaucoma, keratitis, scleritis, maculopathies, retinal degeneration, age related macular degeneration, diabetic retinopathy, ocular sarcoidosis, Vogt-Koyanagi-Harada syndrome, cystoid macular edema, uveitis, Behcet's disease, infections (Syphilis, Lyme, tuberculosis, and toxoplasmosis), subretinal fibrosis, carotid artery disease (CAD), vascular diseases, exudative diseases, trauma, proliferative diabetic retinopathy, bone marrow transplantation retinopathy, viral retinitis, ocular tuberculosis, retinal tears, intraocular lymphoid tumors, myiasis, genetic disorders such as retinitis pigmentosa, Eales disease, parafoveal telangiectasia, and acute retinal pigment epithelitis.

ADVANTAGE - The inserts effectively provide extended or sustained release of therapeutic agents on or into the eye and/or nasolacrimal system of an individual and provide therapeutic effect to the eye which is effective in stabilizing, enhancing or improving the patient's vision. The inserts are relatively easy to manufacture compared to previously described punctual plugs; address patient compliance concerns of administering therapeutic agents to an eye and provide enhancements in the amount of therapeutic agent that may be provided in the drug delivery systems. The insert effectively resolves compliance issues; is easy to administer to the patient; and easy to manufacture. The polymers are biologically inert and non-allergenic; degrade or erode for extended periods of time thus providing sustained drug release from the insert. The insert provides extended release of the therapeutic agent (preferably for more than 1 month, especially for more than 6 months). Dwg.0/5

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A09-A07; A12-V02A; B01-B02; B03-A; B04-C01C;  
B04-C01E; B04-C01H; B04-C03D; B04-H03; B04-N03G;  
B06-A03; B06-D06; B07-E03; B07-F03; B09-D01;  
B11-C04A; B12-M12H; B14-A01A; B14-A01B1A; B14-A03C;  
B14-F02; B14-H01L; B14-N03; B14-N05; B14-N07C;  
B14-N17B; D09-C01

TECH UPTX: 20060421

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (P2) is a steroidal or non-steroidal antiinflammatory agent, retinoid, prostaglandin, tyrosine kinase inhibitor, adrenoreceptor (ant)agonist, dopaminergic agonist, cholinergic agonist, carbonic anhydrase inhibitor, guanylate cyclase activator, cannabinoid, endothelin, adenosine agonist, anti-angiogenic compound, angiostatic compound, neuroprotectant, analgesic, antipyretic, antihistamine, antibiotic, beta blocker, anti-neoplastic agent, immunosuppressive agent, antiviral agent and/or antioxidant (preferably non-steroidal antiinflammatory agent). (P2) is: a combination of brimonidine or its salts and timolol or its salts; at least one of bimatoprost, latanoprost, travoprost, unoprostone isopropyl or their salts; or at least one of cyclosporin and prednisolone acetate, memantine, triamcinolone or their salts (preferably triamcinolone acetate). Preferred Member: The member comprises a head portion structure to be placed in proximity to a punctum, and a body portion structured to be placed in a lacrimal canaliculus. The body portion comprises a distal end and a neck located between the distal end and the head portion, where the distal end has a greater diameter relative to the diameter of the neck. When the member has a peripheral surface, (D1) further comprises a coating located on the peripheral surface except for portions of the peripheral surface, which contact an eye of the individual, where the coating is impermeable to the therapeutic component. The member comprises a distal end structured to be placed in a lacrimal canaliculus, and an aperture in the coating provided at the distal end of the member. Preferred Insert: (D1) In the form of an extrusion-molded member comprises a blend of at least one (P1) and at least one (P2).

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (P1) Comprises at least one biodegradable copolymer or at least one polymer selected from poly lactic acid, poly glycolic acid and their copolymer and derivatives.

L72 ANSWER 16 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2006-612328 [63] WPIX  
CROSS REFERENCE: 2006-352698 [36]  
DOC. NO. CPI: C2006-189048  
TITLE: Use of **cyclosporine** component for the treatment of a human or animal having a condition e.g. systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, maloplakia of the skin.  
DERWENT CLASS: B04  
INVENTOR(S): POWER, D; STERN, M E  
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2006199760	A1	20060907	(200663)*		8	A61K038-12	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006199760	A1 Div ex	US 2004-990054	20041115
		US 2006-429050	20060505

PRIORITY APPLN. INFO: US 2004-990054 20041115; US  
2006-429050 20060505

INT. PATENT CLASSIF.:

MAIN: A61K038-12; A61K038-13

BASIC ABSTRACT:

US2006199760 A UPAB: 20061002

NOVELTY - Treating a human or animal suffering from systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, comprising topically administering a **cyclosporine** component to the subject, is new.

ACTIVITY - Dermatological; Antiinflammatory; Immunosuppressive; Antirheumatic; Antiarthritic; Neuroprotective; Keratolytic; Antipruritic; Antiulcer; Gastrointestinal-Gen.

A male patient (age 51) suffering from ulcerative colitis was treated with a composition containing **cyclosporin A** (0.3 weight%) in a conventional carrier. The composition, in the form of a rectal suppository, was administered once daily for two weeks. After such administration, the patient reports that at least one symptom e.g. pain, associated with the ulcerative colitis was reduced in severity.

MECHANISM OF ACTION - None given.

USE - The method is used for the treatment of a human or animal having a condition e.g. systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, maloplakia of the skin, oral frictional hyperkeratosis, oral manifestations of autoimmune blistering disease, oral lichen planus, aphthous ulcers, nasal polyps, rhinosporidiosis, sinusitis, iritis, carcinoid lung, laryngitis and atrophic gastritis (all claimed), dry mouth syndrome, verruciform xanthoma, achlorhydria, mucous cysts, oral submucous fibrosis, oral nevi, cancer of the oral mucosa, maloplakia of the genito-urinary tract, vulvovaginitis, helicobacter pylori infection, duodenal ulcers, peptic

ulcers, conditions affecting the uterus and appendicitis, inflammatory bowel disease.

ADVANTAGE - The **cyclosporine** component provide substantial overall efficacy in providing the desired therapeutic effect or effects; can be easily and effectively practiced by the prescribing physician and patient without causing substantial or undue patient stress; ease of practice and reduced patient stress. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; GI; DCN  
MANUAL CODES: CPI: B04-C01C; B04-C01H; B12-M12B; B14-A02B3; B14-C09B;  
B14-E10B; B14-G02D; B14-H01; B14-N04; B14-N05;  
B14-N17; B14-S01; B14-S16

TECH UPTX: 20061002  
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The **cyclosporine** component is selected from **cyclosporines** and/or **cyclosporine** derivatives, or their salts and mixtures, especially derivatives of **cyclosporin A**, its salt and mixtures.

L72 ANSWER 17 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2006-352699 [36] WPIX  
DOC. NO. CPI: C2006-115197  
TITLE: Use of **cyclosporin A** component to treat mucin deficiency of mucosal tissue (being located in oral cavity) or dysfunctional mucosal tissue of a human or animal.  
DERWENT CLASS: B04  
INVENTOR(S): **POWER, D; STERN, M E**  
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC  
COUNTRY COUNT: 113  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2006105945	A1	20060518	(200636)*		9	A61K038-12	
WO 2006055418	A1	20060526	(200636)	EN		A61K038-12	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006105945	A1	US 2004-990055	20041115
WO 2006055418	A1	WO 2005-US40928	20051111

PRIORITY APPLN. INFO: US 2004-990055 20041115

INT. PATENT CLASSIF.:

MAIN: A61K038-12; A61K038-13  
SECONDARY: A61P001-00; A61P001-02; A61P001-04; A61P015-00;  
A61P015-02; A61P017-00; A61P035-00

BASIC ABSTRACT:

US2006105945 A UPAB: 20060607



NOVELTY - Treating a mucin deficiency of mucosal tissue and dysfunctional mucosal tissue, comprises topically administering a **cyclosporin A** component (I) to mucosal tissue of a human or animal having a mucin deficiency, the mucosal tissue, being located in an oral cavity of the human or animal.

ACTIVITY - Antiulcer; Antiinflammatory; Cytostatic; Gynecological; Uropathic; Gastrointestinal-Gen.; Dermatological; Antimicrobial.

MECHANISM OF ACTION - None given.

USE - (I) is useful to treat: a mucin deficiency, dysfunctional mucosal tissue (results in a condition of oral submucous fibrosis, oral nevi and cancers of the oral mucosa) of mucosal tissue, located in an oral cavity of a human or animal; and a dry mouth syndrome (claimed). (I) is useful to treat: appendicitis, genito-urinary tract and gastrointestinal tract conditions, verruciform xanthoma, achlorhydria, mucous cysts, maloplakia of the genito-urinary tract, helicobacter pylori infection, duodenal ulcers and peptic ulcers of a human or animal.

ADVANTAGE - (I) is effective in the treatment of mucin deficiency, dysfunctional mucosal tissue and dry mouth syndrome (claimed). (I) provides the treatment without causing substantial or undue patient stress.

Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: B02-C01; B04-C01H; B12-M12N; B14-A01A; B14-E08;  
B14-E10; B14-H01K1; B14-N05; B14-N07

TECH UPTX: 20060607

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (I) is **cyclosporin A**, derivatives of **cyclosporin A** and/or their salts. (I) comprises **cyclosporin A**. The oral rinse includes 0.03-15 (preferably 0.1-5) wt.% of (I). The emulsion includes 0.03-15 (preferably 0.1-5) wt.% of (I).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The human or animal has dry mouth syndrome resulting at least in part from the mucin deficiency and immune inflammation salivary gland secretion variation, the administering is effective in treating the dry mouth syndrome. (I) is administered in an oral rinse or in an emulsion.

L72 ANSWER 18 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2006-352698 [36] WPIX  
CROSS REFERENCE: 2006-612328 [63]  
DOC. NO. CPI: C2006-115196  
TITLE: Treating an inflammatory bowel disease comprises topically administering a **cyclosporin A** component (e.g. **cyclosporin A**) in a rectal suppository.  
DERWENT CLASS: B04  
INVENTOR(S): POWER, D; STERN, M E  
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC  
COUNTRY COUNT: 113  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC																																																											
US 2006105944	A1	20060518	(200636)*		8	A61K038-12																																																												
WO 2006055417	A2	20060526	(200636)	EN		A61K038-12																																																												
RW:	AT	BE	BG	BW	CH	CY	CZ	DE	DK	EA	EE	ES	FI	FR	GB	GH	GM	GR	HU	IE	IS	IT	KE	LS	LT	LU	LV	MC	MW	MZ	NA	NL	OA	PL	PT	RO	SD	SE	SI	SK	SL	SZ	TR	TZ	UG	ZM	ZW																			
W:	AE	AG	AL	AM	AT	AU	AZ	BA	BB	BG	BR	BW	BY	BZ	CA	CH	CN	CO	CR	CU	CZ	DE	DK	DM	DZ	EC	EE	EG	ES	FI	GB	GD	GE	GH	GM	HR	HU	ID	IL	IN	IS	JP	KE	KG	KM	KN	KP	KR	KZ	LC	LK	LR	LS	LT	LU	LV	LY	MA	MD	MG	MK	MN	MW	MX	MZ	NA

NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN  
TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006105944	A1	US 2004-990054	20041115
WO 2006055417	A2	WO 2005-US40926	20051111

PRIORITY APPLN. INFO: US 2004-990054 20041115  
INT. PATENT CLASSIF.:

MAIN: A61K038-12; A61K038-13

BASIC ABSTRACT:

US2006105944 A UPAB: 20061002

NOVELTY - Treating an inflammatory bowel disease in a human or animal comprising topically administering a cyclosporin A component (I) (cyclosporin A and/or its salts) in a rectal suppository to a human or animal, is new.

ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.; Antiulcer; Dermatological; Immunosuppressive; Antiarthritic; Antirheumatic; Neuroprotective; Keratolytic; Antipruritic; Cytostatic.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - (I) is useful for the treatment of an inflammatory bowel disease (ulcerative colitis) (claimed). (I) is useful for the treatment of systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, maloplakia of the skin, oral frictional hyperkeratosis, oral manifestations of autoimmune blistering disease, oral lichen planus, aphthous ulcers, nasal polyps, rhinosporiodosis, sinusitis, iritis, carcinoid lung, laryngitis and atrophic gastritis. (I) was tested for its ability to treat systemic lupus erythematosus in a patient. The results showed that (I) reduced the severity of the systemic lupus erythematosus.

ADVANTAGE - The method can be easily and effectively practiced by the prescribing physician and patient without causing substantial or undue patient stress. The method is effective to treat an inflammatory bowel disease.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-C01B; B04-C01H; B12-M08; B12-M12P; B14-C09B;  
B14-E08; B14-E10B; B14-E10C1; B14-G02D; B14-H01K3;  
B14-N04; B14-N05A; B14-N17; B14-S01

TECH UPTX: 20060607

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The administering step comprises topically administering (I) at or near a tissue area of the human or animal affected by the inflammatory bowel disease (preferably ulcerative colitis). Treating comprises reducing the severity of at least one symptom of the inflammatory bowel disease (preferably ulcerative colitis).

L72 ANSWER 19 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2006-054193 [06] WPIX

DOC. NO. CPI: C2006-020316

TITLE: Liquid, useful to treat dry eye disease, comprises a therapeutically effective concentration of a cyclosporin and a vitamin E tocopherol polyethylene glycol succinate.

DERWENT CLASS: A96 B05

INVENTOR(S): CHANG, J N; GRAHAM, R; TIEN, W L

PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC

COUNTRY COUNT: 111  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2005277584	A1	20051215	(200606)*		5	A61K038-13	
WO 2006001963	A1	20060105	(200606)	EN		A61K009-08	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005277584	A1	US 2004-865638	20040609
WO 2006001963	A1	WO 2005-US18025	20050519

PRIORITY APPLN. INFO: US 2004-865638 20040609  
INT. PATENT CLASSIF.:

MAIN: A61K009-08; A61K038-13  
SECONDARY: A61K031-355; A61K047-22; A61P027-04

BASIC ABSTRACT:

US2005277584 A UPAB: 20060124

NOVELTY - Liquid (I) comprises a therapeutically effective concentration of a **cyclosporin** and a vitamin E tocopherol polyethylene glycol succinate (A) (where (I) is in aqueous solution and no hydrophilic organic solvent is present at a mass concentration greater than half of that of the **cyclosporin**).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a composition (A1) comprising therapeutically effective concentration of a **cyclosporin A** and (A) (where (A1) is in aqueous liquid solution which is intended for ophthalmic use and no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of **cyclosporin A**).

USE - (I) is useful to treat dry eye disease (claimed). (I) is also useful to treat or prevent other conditions or diseases related to immune response, inflammatory response, parasitic and other infection.

ADVANTAGE - (I) has improved bioavailability. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A10-E07; A12-V01; B02-C01; B12-M07; B14-A01;  
B14-A02; B14-B02; B14-C03; B14-G01; B14-N03

TECH UPTX: 20060124

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (I) contains essentially no hydrophilic organic solvent. The vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is at least 8 times that of the **cyclosporin** and the vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is no more than 15 times that of the **cyclosporin**. At least 10 mg of the vitamin E tocopherol polyethylene glycol succinate is present for every mg of the **cyclosporin** present in the solution. The vitamin E tocopherol polyethylene glycol succinate and the **cyclosporin** have a concentration ratio of about 10-1. The vitamin E tocopherol polyethylene glycol succinate is present at a concentration that is no less than 0.5% and the vitamin E tocopherol polyethylene glycol

succinate is present at a concentration that is no greater than 5%. (I) comprises about 0.1% **cyclosporin A** and 1% vitamin E tocopherol polyethylene glycol succinate. (I) comprises **cyclosporin A** which is present at a concentration of at least 0.01% and not greater than 0.2%. (I) is consisting essentially of a therapeutically effective concentration of **cyclosporin A**, an effective amount of a vitamin E tocopherol polyethylene glycol succinate, water and one or more combination of excipients such as buffers, thickening agents, tonicity agents, preservatives or chelating agents. The **cyclosporin A** is present at concentration at or below 1 (preferably less than or equal to 0.15)%. (A1) comprises about 0.05 (preferably 1)% of **cyclosporin A** and vitamin E tocopherol polyethylene glycol succinate.

=> => FILE BIOSIS  
FILE 'BIOSIS' ENTERED AT 16:36:17 ON 02 OCT 2006  
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FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 27 September 2006 (20060927/ED)

=> D QUE L81

L73 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L74 ( 213487)SEA FILE=BIOSIS ABB=ON PLU=ON EYE OR ASTHENOPIA OR CONJUNCTI  
VAL DISEASES OR CORNEAL DISEASES OR EYELID DISEASES OR  
LACRIMAL APPARATUS DISEASES OR LENS DISEASES OR OCULAR  
HYPERTENSION  
L75 ( 7948)SEA FILE=BIOSIS ABB=ON PLU=ON OCULAR HYPOTENSION OR OCULAR  
MOTILITY DISORDERS OR OPTIC NERVE DISEASES OR ORBITAL DISEASES  
OR PUPIL DISORDERS OR REFRACTIVE ERRORS OR RETINAL DISEASES  
OR SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR  
VITREORETINOPATHY OR VITREOUS DETACHMENT  
L76 ( 124285)SEA FILE=BIOSIS ABB=ON PLU=ON OIL  
L77 ( 23151)SEA FILE=BIOSIS ABB=ON PLU=ON EMULSI?  
L78 SEL PLU=ON L73 1- CHEM : 38 TERMS  
L79 ( 46884)SEA FILE=BIOSIS ABB=ON PLU=ON L78  
L80 ( 8)SEA FILE=BIOSIS ABB=ON PLU=ON ((L74 OR L75)) AND L76 AND L77  
AND L79  
L81 8 SEA FILE=BIOSIS ABB=ON PLU=ON L80 NOT PY>2004

=> S L81 NOT L14

L134 8 L81 NOT L14

=> FILE EMBASE

FILE 'EMBASE' ENTERED AT 16:36:48 ON 02 OCT 2006  
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FILE COVERS 1974 TO 2 Oct 2006 (20061002/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default)  
and biweekly.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> D QUE L94

L82 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L83 SEL PLU=ON L82 1- CHEM : 38 TERMS  
L84 ( 74476)SEA FILE=EMBASE ABB=ON PLU=ON L83  
L85 ( 301867)SEA FILE=EMBASE ABB=ON PLU=ON EYE DISEASE+NT/CT  
L86 ( 5657)SEA FILE=EMBASE ABB=ON PLU=ON OIL/CT  
L87 ( 46238)SEA FILE=EMBASE ABB=ON PLU=ON D3.60.650./CT  
L88 ( 225955)SEA FILE=EMBASE ABB=ON PLU=ON L85/MAJ  
L89 ( 22)SEA FILE=EMBASE ABB=ON PLU=ON L88 AND L84 AND ((L86 OR L87))

L90 ( 17)SEA FILE=EMBASE ABB=ON PLU=ON L89 NOT PY>2004  
 L91 ( 416)SEA FILE=EMBASE ABB=ON PLU=ON L84(L)TP/CT  
 L92 ( 12)SEA FILE=EMBASE ABB=ON PLU=ON L91 AND L85 AND ((L86 OR L87))  
 L93 ( 9)SEA FILE=EMBASE ABB=ON PLU=ON L92 NOT PY>2004  
 L94 21 SEA FILE=EMBASE ABB=ON PLU=ON L90 OR L93

=> S L94 NOT L30  
 L135 21 L94 NOT L30

=> FILE HCAPLUS

FILE 'HCAPLUS' ENTERED AT 16:37:21 ON 02 OCT 2006  
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FILE COVERS 1907 - 2 Oct 2006 VOL 145 ISS 15  
 FILE LAST UPDATED: 1 Oct 2006 (20061001/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> D QUE L111

L95 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
 L96 ( 36733)SEA FILE=HCAPLUS ABB=ON PLU=ON EYE, DISEASE+OLD,NT/CT  
 L97 ( 24550)SEA FILE=HCAPLUS ABB=ON PLU=ON EMULSIFYING AGENTS/CT  
 L98 ( 388102)SEA FILE=HCAPLUS ABB=ON PLU=ON OILS+OLD,NT/CT  
 L99 SEL PLU=ON L95 1- CHEM : 38 TERMS  
 L100( 23233)SEA FILE=HCAPLUS ABB=ON PLU=ON L99  
 L101( 2)SEA FILE=HCAPLUS ABB=ON PLU=ON L100 AND L96 AND L97 AND L98  
 L102( 4)SEA FILE=HCAPLUS ABB=ON PLU=ON L96 AND L100 AND L97  
 L103( 17)SEA FILE=HCAPLUS ABB=ON PLU=ON L96 AND L100 AND L98  
 L104( 28869)SEA FILE=HCAPLUS ABB=ON PLU=ON EMULSIONS/CT  
 L105( 1)SEA FILE=HCAPLUS ABB=ON PLU=ON L96 AND L100 AND L104 AND L98  
 L106( 2)SEA FILE=HCAPLUS ABB=ON PLU=ON L96 AND L100 AND L104  
 L107( 20)SEA FILE=HCAPLUS ABB=ON PLU=ON (L101 OR L102 OR L103 OR L105 OR L106)  
 L108( 19)SEA FILE=HCAPLUS ABB=ON PLU=ON L107 AND PATENT/DT  
 L109( 1)SEA FILE=HCAPLUS ABB=ON PLU=ON L107 NOT L108  
 L110( 19)SEA FILE=HCAPLUS ABB=ON PLU=ON ((L108 OR L109)) NOT (PRY>2004 OR PR>2004)  
 L111 18 SEA FILE=HCAPLUS ABB=ON PLU=ON L110 NOT LIPOSOMAL COCHLEATE/T  
 I

=> S L111 NOT L44  
L136 17 L111 NOT L44

=> FILE MEDLINE  
FILE 'MEDLINE' ENTERED AT 16:37:49 ON 02 OCT 2006

FILE LAST UPDATED: 30 Sep 2006 (20060930/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)  
[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_med\\_data\\_changes.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html)  
[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_2006\\_MeSH.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html)

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> D QUE L122  
L112( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L113( 9221)SEA FILE=MEDLINE ABB=ON PLU=ON EMULSIONS+NT/CT  
L114( 124)SEA FILE=MEDLINE ABB=ON PLU=ON EMULSIFYING AGENTS/CT  
L115( 34652)SEA FILE=MEDLINE ABB=ON PLU=ON OILS+NT/CT  
L116 SEL PLU=ON L112 1- CHEM : 38 TERMS  
L117( 39885)SEA FILE=MEDLINE ABB=ON PLU=ON L116  
L118( 320609)SEA FILE=MEDLINE ABB=ON PLU=ON EYE DISEASES+NT/CT  
L119( 1)SEA FILE=MEDLINE ABB=ON PLU=ON L118 AND L117 AND ((L113 OR L114)). AND L115  
L120( 19)SEA FILE=MEDLINE ABB=ON PLU=ON L118 AND L117 AND ((L113 OR L114))  
L121( 4)SEA FILE=MEDLINE ABB=ON PLU=ON L118 AND L117 AND L115  
L122 16 SEA FILE=MEDLINE ABB=ON PLU=ON ((L119 OR L120 OR L121)) NOT PY>2004

=> S L122 NOT L62  
L137 14 L122 NOT L62

=> FILE WPIX  
FILE 'WPIX' ENTERED AT 16:38:39 ON 02 OCT 2006  
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FILE LAST UPDATED: 2 OCT 2006 <20061002/UP>  
MOST RECENT DERWENT UPDATE: 200663 <200663/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://scientific.thomson.com/support/patents/coverage/latestupdates/>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE  
[http://www.stn-international.de/stndatabases/details/ipc\\_reform.html](http://www.stn-international.de/stndatabases/details/ipc_reform.html) and  
<http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf> <<<

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INDEX ENHANCEMENTS PLEASE VISIT:  
[http://www.stn-international.de/stndatabases/details/dwpi\\_r.html](http://www.stn-international.de/stndatabases/details/dwpi_r.html) <<<  
'BI,ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> D QUE L133

L123( 1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN  
L124( 73228)SEA FILE=WPIX ABB=ON PLU=ON EYE/BI,ABEX OR ASTHENOPIA/BI,ABE  
X OR CONJUNCTIVAL DISEASES/BI,ABEX OR CORNEAL DISEASES/BI,ABEX  
OR EYELID DISEASES/BI,ABEX OR LACRIMAL APPARATUS DISEASES/BI,AB  
EX OR LENS DISEASES/BI,ABEX OR OCULAR HYPERTENSION/BI,ABEX  
L125( 650)SEA FILE=WPIX ABB=ON PLU=ON OCULAR HYPOTENSION/BI,ABEX OR  
OCULAR MOTILITY DISORDERS/BI,ABEX OR OPTIC NERVE DISEASES/BI,AB  
EX OR ORBITAL DISEASES/BI,ABEX OR PUPIL DISORDERS/BI,ABEX OR  
REFRACTIVE ERRORS/BI,ABEX OR RETINAL DISEASES/BI,ABEX OR  
SCLERAL DISEASES/BI,ABEX OR UVEAL DISEASES/BI,ABEX OR VISION  
DISORDERS/BI,ABEX OR VITREORETINOPATHY/BI,ABEX OR VITREOUS  
DETACHMENT/BI,ABEX  
L126( 444197)SEA FILE=WPIX ABB=ON PLU=ON OIL/BI,ABEX  
L127( 169370)SEA FILE=WPIX ABB=ON PLU=ON EMULSI?/BI,ABEX OR (A10-B03 OR  
B12-M03 OR C12-M03 OR A12-B01A)/MC  
L128( 598)SEA FILE=WPIX ABB=ON PLU=ON (K04-E01 OR H06-B09 OR G06-F01B)/  
MC  
L129 SEL PLU=ON L123 1- CHEM : 38 TERMS  
L130( 2231)SEA FILE=WPIX ABB=ON PLU=ON L129  
L131( 959)SEA FILE=WPIX ABB=ON PLU=ON RA0135/DCN OR 90981-1-0-0/DCRE  
L132( 20)SEA FILE=WPIX ABB=ON PLU=ON ((L130 OR L131)) AND ((L124 OR  
L125)) AND L126 AND ((L127 OR L128))  
L133 17 SEA FILE=WPIX ABB=ON PLU=ON L132 NOT PRY>2004

=> S L133 NOT L71

L138 16 L133 NOT L71

=> DUP REM L137 L134 L135 L138 L136  
FILE 'MEDLINE' ENTERED AT 16:39:41 ON 02 OCT 2006

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PROCESSING COMPLETED FOR L134  
PROCESSING COMPLETED FOR L135



PROCESSING COMPLETED FOR L138

PROCESSING COMPLETED FOR L136

L139 73 DUP REM L137 L134 L135 L138 L136 (3 DUPLICATES REMOVED)

ANSWERS '1-14' FROM FILE MEDLINE

ANSWERS '15-21' FROM FILE BIOSIS

ANSWERS '22-41' FROM FILE EMBASE

ANSWERS '42-57' FROM FILE WPIX

ANSWERS '58-73' FROM FILE HCAPLUS

=> D IALL 1-14; D IALL 15-21; D IALL 22-41; D IALL ABEQ TECH 42-57; D IBIB ED ABS  
58-73

L139 ANSWER 1 OF 73 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2000269229 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 10811092

TITLE: Efficacy and safety of **cyclosporin A**  
ophthalmic emulsion in the treatment of moderate-to-severe  
dry eye disease: a dose-ranging, randomized trial. The  
**Cyclosporin A** Phase 2 Study Group.

AUTHOR: Stevenson D; Tauber J; Reis B L

CORPORATE SOURCE: Mercy Hospital, New Orleans, Louisiana, USA.

SOURCE: Ophthalmology, (2000 May) Vol. 107, No. 5, pp. 967-74.

Journal code: 7802443. ISSN: 0161-6420.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200005

ENTRY DATE: Entered STN: 25 May 2000

Last Updated on STN: 25 May 2000

Entered Medline: 18 May 2000

ABSTRACT:

OBJECTIVE: To investigate the efficacy, safety, formulation tolerability, and optimal dosing of a novel **cyclosporin A** oil-in-water emulsion formulation for the treatment of moderate-to-severe dry eye disease. DESIGN: Randomized, multicenter, double-masked, parallel-group, dose-response controlled trial. PARTICIPANTS: Total enrollment: 162 patients; \*\*\*cyclosporin\*\*\* A groups: 129 patients; vehicle group: 33 patients. INTERVENTION: Patients instilled study medication (\*\*\*cyclosporin\*\*\* A ophthalmic emulsion 0.05%, 0.1%, 0.2%, or 0.4%, or vehicle) twice daily into both eyes for 12 weeks, followed by a 4-week posttreatment observation period. MAIN OUTCOME MEASURES: Efficacy: rose bengal staining, superficial punctate keratitis, Schirmer tear test, symptoms of ocular discomfort, and the Ocular Surface Disease Index (OSDI; a measure of symptom frequency and impact on vision-related functioning). Safety: biomicroscopy, **cyclosporin A** blood levels, conjunctival microbiology, intraocular pressure, visual acuity, and monitoring of adverse events. RESULTS: In a subset of 90 patients with moderate-to-severe keratoconjunctivitis sicca, the most significant improvements with \*\*\*cyclosporin\*\*\* A treatment were in rose bengal staining, superficial punctate keratitis, sandy or gritty feeling, dryness, and itching, with improvements persisting into the posttreatment period in some treatment groups. There was also a decrease in OSDI scores, indicating a decrease in the effect of ocular symptoms on patients' daily lives. There was no clear dose-response relationship, but **cyclosporin A** 0.1% produced the most consistent improvement in objective and subjective end points and \*\*\*cyclosporin\*\*\* A 0.05% gave the most consistent improvement in

patient symptoms. The vehicle also performed well, perhaps because of its long residence time on the ocular surface. There were no significant adverse effects, no microbial overgrowth, and no increased risk of ocular infection in any treatment group. The highest cyclosporin A blood concentration detected was 0.16 ng/ml. All treatments were well tolerated by patients. CONCLUSIONS: Cyclosporin A ophthalmic emulsions, 0.05%, 0.1%, 0.2%, and 0.4%, were safe and well tolerated, significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning. \*\*\*Cyclosporin\*\*\* A 0.05% and 0.1% were deemed the most appropriate formulations for future clinical studies because no additional benefits were observed with the higher concentrations.

CONTROLLED TERM: Check Tags: Female; Male  
Adult  
Aged  
Aged, 80 and over  
\*Cyclosporine: AD, administration & dosage  
Cyclosporine: AE, adverse effects  
Dose-Response Relationship, Drug  
Double-Blind Method  
\*Dry Eye Syndromes: DT, drug therapy  
Dry Eye Syndromes: ME, metabolism  
Dry Eye Syndromes: PP, physiopathology  
Emulsions  
Humans  
Intraocular Pressure  
Middle Aged  
Ophthalmic Solutions: AD, administration & dosage  
Ophthalmic Solutions: AE, adverse effects  
Research Support, Non-U.S. Gov't  
Safety  
Tears: SE, secretion  
Visual Acuity

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 2 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 2004493329 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 15461545  
TITLE: Topical 0.05% cyclosporin in the treatment of dry eye.  
AUTHOR: Perry Henry D; Donnenfeld Eric D  
CORPORATE SOURCE: North Shore University Hospital, Department of Ophthalmology, Long Island Jewish Medical Centre, Great Neck, New York, USA.. hankcornea@aol.com  
SOURCE: Expert opinion on pharmacotherapy, (2004 Oct) Vol. 5, No. 10, pp. 2099-107. Ref: 24  
Journal code: 100897346. E-ISSN: 1744-7666.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200506  
ENTRY DATE: Entered STN: 6 Oct 2004  
Last Updated on STN: 3 Jun 2005  
Entered Medline: 2 Jun 2005

ABSTRACT:  
Dry eye disease is a common and often underdiagnosed condition that affects > 10% of the adult population, > 65 years of age in the US. This condition has

been classified into two separate, but overlapping, categories--aqueous deficiency and evaporative loss. Diagnosis is confused by the lack of a single diagnostic test. Fluorescein break-up time is one of the best screening tests and is augmented by Lissamine green supravital staining. New concepts of pathogenesis have shown that dry eye disease appears to be caused by inflammation mediated by T-cell lymphocytes. This finding led to the study and FDA-approval of topical 0.05% **cyclosporin A** (

\*\*\*Restasis\*\*\* ) for the treatment of dry eye disease. 0.05% \*\*\*Cyclosporin\*\*\* A offers the first therapeutic treatment for patients with moderate-to-severe dry eye disease due to aqueous deficiency.

CONTROLLED TERM: Administration, Topical  
\*Anti-Inflammatory Agents, Non-Steroidal: AD,  
administration & dosage  
Clinical Trials, Phase III

\*Cyclosporine: AD, administration & dosage

Dry Eye Syndromes: CL, classification

Dry Eye Syndromes: DI, diagnosis

\*Dry Eye Syndromes: DT, drug therapy

Dry Eye Syndromes: ET, etiology

Dry Eye Syndromes: IM, immunology

Emulsions

Humans

\*Immunosuppressive Agents: AD, administration & dosage  
Ophthalmic Solutions

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)

CHEMICAL NAME: 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Emulsions);  
0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 3 OF 73

MEDLINE on STN

ACCESSION NUMBER: 2003313129 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12843889

TITLE: [Flow cytometry in impression cytology during  
keratoconjunctivitis sicca: effects of topical  
**cyclosporin A** on HLA DR expression].

Cytofluorimetrie sur empreintes conjonctivales au cours de  
la keratoconjunctivite seche: effets de la ciclosporine  
topique sur l'expression d'antigene HLA DR.

AUTHOR: Galatoire O; Baudouin C; Pisella P J; Brignole F

CORPORATE SOURCE: Service d'Ophtalmologie 3, Hopital des Quinze-Vingts, 28,  
rue de Charenton, 75012 Paris.

SOURCE: Journal francais d'ophtalmologie, (2003 Apr) Vol. 26, No.  
4, pp. 337-43.

Journal code: 7804128. ISSN: 0181-5512.

PUB. COUNTRY: France

DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200308

ENTRY DATE: Entered STN: 5 Jul 2003

Last Updated on STN: 21 Aug 2003

Entered Medline: 20 Aug 2003

ABSTRACT:

PURPOSE: Immune-based inflammation has been observed as a common mechanism of keratoconjunctivitis sicca (KCS). In KCS-affected eyes, up-regulated expression of HLA DR by conjunctival epithelial cells has been demonstrated in impression cytology (IC) specimens using a technique of flow cytometry. The purpose of this study was to monitor the effects of topical **cyclosporin**

\*\*\*A\*\*\* on the expression of this marker over a 12-month period of treatment. METHODS: Patients with moderate-to-severe KCS included in a large European multicenter clinical trial (Cyclosporin Dry Eye Study, Allergan, Irvine, CA) underwent collection of IC specimens at baseline, month 3, month 6, and month 12. They randomly received 0.05% or 0.1% cyclosporin \*\*\*A\*\*\* or vehicle. Patients randomized to receive vehicle received 0.1% \*\*\*cyclosporin\*\*\* A from month 6 onwards. Specimens were processed and analyzed in a masked manner by flow cytometry, using monoclonal antibodies directed to HLA DR. RESULTS: We included 169 patients in this study. HLA DR expression, both in percentage of positive cells and level of expression, was highly significantly reduced after 0.05% and 0.1% cyclosporin \*\*\*A\*\*\* treatment at months 3, 6, and 12 compared with baseline values, whereas vehicle did not induce any change in HLA DR expression over time. The 0.05% and 0.1% cyclosporin emulsions were significantly more effective than the vehicle in reducing HLA DR at months 3 and 6 (0.05%) and at month 6 (0.1%). CONCLUSIONS: Topical cyclosporin A strikingly reduced HLA DR, whereas the vehicle, used as a control tear substitute, had almost no effect. This study confirms that cyclosporin \*\*\*A\*\*\* may be effective in reducing conjunctival inflammation in moderate-to-severe KCS and is consistent with clinical results in this indication.

CONTROLLED TERM: Check Tags: Female; Male  
Administration, Topical  
Adolescent  
Adult  
Aged  
Aged, 80 and over  
Cyclosporine: AD, administration & dosage  
\*Cyclosporine: TU, therapeutic use  
Double-Blind Method  
Emulsions  
English Abstract  
\*Flow Cytometry  
Fluorescent Antibody Technique, Indirect  
\*HLA-DR Antigens: BI, biosynthesis  
HLA-DR Antigens: GE, genetics  
Humans  
\*Keratoconjunctivitis Sicca: DT, drug therapy  
Keratoconjunctivitis Sicca: IM, immunology  
Keratoconjunctivitis Sicca: PA, pathology  
Middle Aged  
Ophthalmic Solutions  
Prospective Studies  
Sjogren's Syndrome: CO, complications  
Sjogren's Syndrome: IM, immunology  
Sjogren's Syndrome: PA, pathology  
Treatment Outcome  
Vehicles

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions); 0 (HLA-DR Antigens); 0 (Ophthalmic Solutions); 0 (Vehicles)

L139 ANSWER 4 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 2003200578 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 12718570  
TITLE: Cyclosporin - allergan. Ciclosporin - allergan, cyclosporin ophthalmic emulsion, cyclosporine - Allergan, Restasis.  
AUTHOR: Anonymous  
SOURCE: Drugs in R&D, (2003) Vol. 4, No. 2, pp. 126-7.

Journal code: 100883647. ISSN: 1174-5886.  
PUB. COUNTRY: New Zealand  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE III)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200311  
ENTRY DATE: Entered STN: 1 May 2003  
Last Updated on STN: 17 Dec 2003  
Entered Medline: 18 Nov 2003  
CONTROLLED TERM: \*Cyclosporine: AE, adverse effects  
Drugs, Investigational  
Emulsions  
\*Eye Diseases: DT, drug therapy  
Humans  
Immunosuppressive Agents: AE, adverse effects  
Ophthalmic Solutions: AE, adverse effects  
\*Ophthalmic Solutions: TU, therapeutic use  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Drugs, Investigational); 0 (Emulsions); 0  
(Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 5 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 2004024662 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 14723112  
TITLE: Considerations in the pharmacoeconomics of dry eye.  
AUTHOR: Hirsch Jan D  
CORPORATE SOURCE: Prescription Solution, Cost Mesa, Calif., USA.  
SOURCE: Managed care (Langhorne, Pa.), (2003 Dec) Vol. 12, No. 12  
Suppl, pp. 33-8.  
Journal code: 9303583. ISSN: 1062-3388.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Health  
ENTRY MONTH: 200403  
ENTRY DATE: Entered STN: 16 Jan 2004  
Last Updated on STN: 10 Mar 2004  
Entered Medline: 9 Mar 2004

ABSTRACT:  
Dry eye disease diminishes the quality of patients' lives and drives  
utilization of health care resources. Until recently, all treatments for dry  
eye have been palliative. A new treatment, **cyclosporine A**  
ophthalmic emulsion, addresses the disease's underlying causes. It warrants  
pharmacoeconomic analysis to determine its place in managed care.

CONTROLLED TERM: Check Tags: Female; Male  
Anti-Inflammatory Agents: EC, economics  
Anti-Inflammatory Agents: TU, therapeutic use  
Cost of Illness  
Cyclosporine: EC, economics  
\*Cyclosporine: TU, therapeutic use  
\*Dry Eye Syndromes: DT, drug therapy  
Dry Eye Syndromes: EC, economics  
Dry Eye Syndromes: PP, physiopathology  
Economics, Pharmaceutical  
Emulsions  
Humans  
\*Managed Care Programs: EC, economics  
Middle Aged

Ophthalmic Solutions: EC, economics  
Ophthalmic Solutions: TU, therapeutic use  
Palliative Care  
Quality of Life  
Questionnaires  
Treatment Outcome

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Anti-Inflammatory Agents); 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 6 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 2000228811 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 10768324  
TITLE: 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.  
AUTHOR: Sall K; Stevenson O D; Mundorf T K; Reis B L  
CORPORATE SOURCE: Sall Eye Surgery Center, Bellflower, California, USA.  
SOURCE: Ophthalmology, (2000 Apr) Vol. 107, No. 4, pp. 631-9. Journal code: 7802443. ISSN: 0161-6420.  
COMMENT: Erratum in: Ophthalmology 2000 Jul;107(7):1220  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 27 Apr 2000  
Last Updated on STN: 22 Sep 2000  
Entered Medline: 18 Apr 2000

ABSTRACT:

OBJECTIVE: To compare the efficacy and safety of cyclosporin \*\*\*A\*\*\* ([CsA] 0.05% and 0.1% ophthalmic emulsions) to vehicle in patients with moderate to severe dry eye disease. DESIGN: Multicenter, randomized, double-masked, parallel-group, 6-month, vehicle-controlled. PARTICIPANTS: A total of 877 patients with defined moderate to severe dry eye disease (292 to 293 in each treatment group). METHODS: Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis. MAIN OUTCOME MEASURES: Efficacy: corneal and interpalpebral dye staining, Schirmer tear test (with and without anesthesia), tear break-up time, Ocular Surface Disease Index (OSDI), facial expression, patient subjective rating scale, symptoms of dry eye, investigator's evaluation of global response to treatment, treatment success, and daily use of artificial tears. Safety: occurrence of adverse events, best-corrected visual acuity, intraocular pressure, biomicroscopy, and blood trough CsA concentrations. RESULTS: Treatment with CsA, 0.05% or 0.1%, gave significantly ( $P < \text{or} = 0.05$ ) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements ( $P < 0.05$ ) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose-response effect. Both CsA treatments exhibited an excellent safety profile, and there were no significant topical or systemic adverse safety findings. CONCLUSIONS: The novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both objective and subjective measures. Topical CsA represents a new pharmacologically based

treatment for dry eye disease that may provide significant patient benefits.

CONTROLLED TERM: Check Tags: Female; Male  
Comparative Study  
Cornea: DE, drug effects  
Cyclosporine: AD, administration & dosage  
Cyclosporine: AE, adverse effects  
\*Cyclosporine: TU, therapeutic use  
Double-Blind Method  
Drug Evaluation  
\*Dry Eye Syndromes: DT, drug therapy  
Emulsions  
Humans  
Intraocular Pressure  
Middle Aged  
Ophthalmic Solutions: AD, administration & dosage  
Ophthalmic Solutions: AE, adverse effects  
\*Ophthalmic Solutions: TU, therapeutic use  
Research Support, Non-U.S. Gov't  
Safety  
Tears: ME, metabolism  
Visual Acuity

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 7 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 2001033774 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 10928765  
TITLE: Interleukin-6 levels in the conjunctival epithelium of patients with dry eye disease treated with cyclosporine ophthalmic emulsion.  
AUTHOR: Turner K; Pflugfelder S C; Ji Z; Feuer W J; Stern M; Reis B L  
CORPORATE SOURCE: Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Florida 33136, USA.  
SOURCE: Cornea, (2000 Jul) Vol. 19, No. 4, pp. 492-6.  
Journal code: 8216186. ISSN: 0277-3740.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200011  
ENTRY DATE: Entered STN: 22 Mar 2001  
Last Updated on STN: 22 Mar 2001  
Entered Medline: 30 Nov 2000

ABSTRACT:

PURPOSE: To evaluate interleukin-6 (IL-6) levels in the conjunctival epithelium of patients with moderate to severe dry eye disease before and after treatment with cyclosporin A ophthalmic emulsion (CsA) or its vehicle. METHODS: Conjunctival cytology specimens were obtained from a subset of patients enrolled in a 6-month randomized, double-masked clinical trial of the efficacy and safety of topical CsA at baseline and after 3 and 6 months of B.I.D. treatment with 0.05% cyclosporine emulsion (n = 13), 0.1% \*\*\*cyclosporine\*\*\* emulsion (n = 8), or vehicle (n = 10). RNA was extracted and a competitive reverse transcriptase polymerase chain reaction (RT-PCR) was used to evaluate the levels of mRNA encoding the inflammatory cytokine IL-6 and a housekeeping gene, G3PDH. Levels of IL-6 and G3PDH were measured and compared. RESULTS: There was no change from baseline in the level of G3PDH

after 3 or 6 months in any group. IL-6 normalized for G3PDH (IL-6/G3PDH ratio) was not different from baseline at 3 months but showed a significant decrease from baseline in the group treated with 0.05% CsA (p = 0.048) at 6 months. No significant between-group differences were noted and no correlation was observed between the change in IL-6/G3PDH and corneal fluorescein staining. CONCLUSIONS: This preliminary, small-cohort study showed a decrease in IL-6 in the conjunctival epithelium of moderate to severe dry eye patients treated with 0.05% CsA for 6 months. The observed decrease suggests that dry eye disease involves immune-mediated inflammatory processes that may be decreased by treatment with topical ophthalmic **cyclosporine**.

CONTROLLED TERM: Administration, Topical  
Biological Markers  
Comparative Study  
\*Conjunctiva: ME, metabolism  
Conjunctiva: PA, pathology  
\*Cyclosporine: TU, therapeutic use  
DNA Primers: CH, chemistry  
Double-Blind Method  
\*Dry Eye Syndromes: DT, drug therapy  
Dry Eye Syndromes: ME, metabolism  
Dry Eye Syndromes: PA, pathology  
Emulsions  
\*Epithelium: ME, metabolism  
Epithelium: PA, pathology  
Glyceraldehyde-3-Phosphate Dehydrogenases: ME, metabolism  
Humans  
\*Immunosuppressive Agents: TU, therapeutic use  
Interleukin-6: GE, genetics  
\*Interleukin-6: ME, metabolism  
Prospective Studies  
RNA, Messenger: ME, metabolism  
Research Support, Non-U.S. Gov't  
Reverse Transcriptase Polymerase Chain Reaction

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Biological Markers); 0 (DNA Primers); 0 (Emulsions); 0 (Immunosuppressive Agents); 0 (Interleukin-6); 0 (RNA, Messenger); EC 1.2.1.- (Glyceraldehyde-3-Phosphate Dehydrogenases)

L139 ANSWER 8 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 1999410206 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 10482480  
TITLE: **Ciclosporin** microemulsion preconcentrate treatment of patients with Behcet's disease.  
AUTHOR: Fujino Y; Joko S; Masuda K; Yagi I; Kogure M; Sakai J; Usui M; Kotake S; Matsuda H; Ikeda E; Mochizuki M; Nakamura S; Ohno S  
CORPORATE SOURCE: Department of Ophthalmology, University of Tokyo School of Medicine, Japan.  
SOURCE: Japanese journal of ophthalmology, (1999 Jul-Aug) Vol. 43, No. 4, pp. 318-26.  
Journal code: 0044652. ISSN: 0021-5155.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE III)  
(CONTROLLED CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals



ENTRY MONTH: 199909  
ENTRY DATE: Entered STN: 12 Oct 1999  
Last Updated on STN: 12 Oct 1999  
Entered Medline: 29 Sep 1999

ABSTRACT:

PURPOSE: The new microemulsion preconcentrate (MEPC) formulation of \*\*\*cyclosporin\*\*\* has been developed to reduce problems in intestinal absorption and to stabilize fluctuations in blood levels. A multicenter, open-label clinical trial of MEPC was conducted to assess its efficacy and safety in Behcet's disease patients with ocular involvement. METHODS: The patient population comprised 17 de novo patients (patients not previously treated with cyclosporin in the currently available formulation) and 30 patients whose cyclosporin formulation was switched from the conventional formulation to MEPC. The patients were treated with the test formulation for 16 weeks in the former (de novo) group and for 12 weeks in the latter (switched) group. RESULTS: In the de novo group, ocular attacks decreased significantly as compared to the pretreatment incidence in 11 of the 14 patients (78.6%) evaluated after MEPC therapy. Ocular attacks also decreased significantly in the switched group. In the de novo group, visual acuity improved with MEPC therapy in 20 of the 28 eyes (71.4%) examined, and the overall efficacy evaluation was "improved" or "markedly improved" in 13 of the 16 patients evaluated (81.3%). The one case each of onset of neuro-Behcet's disease and intestinal Behcet's disease observed in the de novo group were regarded as adverse reactions. CONCLUSION: It was concluded that \*\*\*cyclosporin\*\*\* MEPC is useful for controlling the ocular symptoms of Behcet's disease, and that it can be used as effectively and safely as the conventional formulation.

CONTROLLED TERM: Check Tags: Female; Male  
Adult  
Aged  
\*Behcet Syndrome: DT, drug therapy  
Behcet Syndrome: ME, metabolism  
Biological Availability  
Cyclosporine: AE, adverse effects  
Cyclosporine: PK, pharmacokinetics  
\*Cyclosporine: TU, therapeutic use  
Drug Evaluation  
Emulsions  
Humans  
Immunosuppressive Agents: AE, adverse effects  
Immunosuppressive Agents: PK, pharmacokinetics  
\*Immunosuppressive Agents: TU, therapeutic use  
Middle Aged  
Pharmaceutical Preparations  
Safety  
Treatment Outcome

CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions); 0 (Immunosuppressive Agents); 0  
(Pharmaceutical Preparations)

L139 ANSWER 9 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 1998426790 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 9754182  
TITLE: A randomized, placebo-controlled trial of topical  
cyclosporin A in steroid-dependent atopic  
keratoconjunctivitis.  
AUTHOR: Hingorani M; Moodaley L; Calder V L; Buckley R J; Lightman  
S  
CORPORATE SOURCE: Moorfields Eye Hospital, London, United Kingdom.  
SOURCE: Ophthalmology, (1998 Sep) Vol. 105, No. 9, pp. 1715-20.

Journal code: 7802443. ISSN: 0161-6420.

PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199810  
ENTRY DATE: Entered STN: 21 Oct 1998  
Last Updated on STN: 21 Oct 1998  
Entered Medline: 13 Oct 1998

ABSTRACT:

OBJECTIVE: This study aimed to investigate the therapeutic effect of topical \*\*\*cyclosporin\*\*\* A (CsA) 2% in maize oil as a steroid-sparing agent in steroid-dependent atopic keratoconjunctivitis. DESIGN: Prospective, randomized, double-masked, placebo-controlled trial. PARTICIPANTS: Twenty-one patients with steroid-dependent atopic keratoconjunctivitis were studied. INTERVENTION: Patients used either topical CsA or vehicle four times daily for 3 months in addition to their usual therapy, and the clinical response was used to taper or stop topical steroids when possible. MAIN OUTCOME MEASURES: Steroid drop usage per week, ability to cease steroid use, scores for symptoms and clinical signs, drop side effects, and overall subjective rating of trial drop by patients and clinician were measured. RESULTS: Cyclosporin \*\*\*A\*\*\* had a greater steroid-sparing effect than did placebo. Nine of 12 CsA patients ceased steroids compared to 1 of 9 placebo patients (P = 0.01), the final steroid use was lower in the CsA group (2.6 +/- 1.4 vs. 27.7 +/- 17.7, P = 0.005), and the mean reduction in steroid use was greater for CsA (85.5 +/- 14.7 vs. 13.9 +/- 16.0, P = 0.005). Clinical signs and symptom scores were reduced to a greater level for CsA. Serious side effects were lid skin maceration in one patient using CsA and an allergic reaction in one placebo patient. Marked blurring of vision after drop instillation was common in both groups, but intense stinging was more common in CsA patients (9/12 vs. 1/9, P = 0.01), limiting frequency of drop use. The clinician rated the trial drops as good or excellent more frequently for CsA (11/12 vs. 0/9, P < 0.0001). CONCLUSIONS: Topical CsA is an effective and safe steroid-sparing agent in atopic keratoconjunctivitis and, despite difficulties in patient tolerance, also improves symptoms and signs.

CONTROLLED TERM: Check Tags: Female; Male  
Administration, Topical  
Adult  
\*Conjunctivitis, Allergic: DT, drug therapy  
Corn Oil: AD, administration & dosage  
\*Cyclosporine: AD, administration & dosage  
Cyclosporine: AE, adverse effects  
Double-Blind Method  
Drug Carriers  
\*Glucocorticoids: TU, therapeutic use  
Humans  
\*Immunosuppressive Agents: AD, administration & dosage  
Immunosuppressive Agents: AE, adverse effects  
Ophthalmic Solutions  
Prospective Studies  
Safety  
Treatment Outcome  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine); 8001-30-7 (Corn Oil)  
CHEMICAL NAME: 0 (Drug Carriers); 0 (Glucocorticoids); 0  
(Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 10 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 1998298735 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9634996  
TITLE: A dose-ranging clinical trial to assess the safety and efficacy of **cyclosporine** ophthalmic emulsion in patients with keratoconjunctivitis sicca. The **Cyclosporine** Study Group.  
AUTHOR: Tauber J  
SOURCE: Advances in experimental medicine and biology, (1998) Vol. 438, pp. 969-72.  
Journal code: 0121103. ISSN: 0065-2598.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199809  
ENTRY DATE: Entered STN: 25 Sep 1998  
Last Updated on STN: 25 Sep 1998  
Entered Medline: 15 Sep 1998  
CONTROLLED TERM: Administration, Topical  
Cyclosporine: AD, administration & dosage  
Cyclosporine: BL, blood  
\*Cyclosporine: TU, therapeutic use  
Dose-Response Relationship, Drug  
Double-Blind Method  
Emulsions  
Humans  
\*Keratoconjunctivitis Sicca: DT, drug therapy  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine)  
CHEMICAL NAME: 0 (Emulsions)

L139 ANSWER 11 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 1998042343 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 9374930  
TITLE: **Neoral**--new **cyclosporin** for old?..  
AUTHOR: Somerville M F; Scott D G  
CORPORATE SOURCE: Rheumatology Department, Norfolk & Norwich Health Care NHS Trust, Norwich.  
SOURCE: British journal of rheumatology, (1997 Oct) Vol. 36, No. 10, pp. 1113-5.  
Journal code: 8302415. ISSN: 0263-7103.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199712  
ENTRY DATE: Entered STN: 9 Jan 1998  
Last Updated on STN: 9 Jan 1998  
Entered Medline: 15 Dec 1997

ABSTRACT:

**Cyclosporin A** is now well established as an effective second-line drug to treat rheumatoid arthritis. In April 1995, the microemulsion-based formulation of **cyclosporin** (**Neoral**) was introduced based on its increased bioavailability at 'no extra cost'. There may have been concerns that with increased bioavailability of **Neoral**, some patients might experience increased toxicity, particularly if transferring from **Sandimmun** to **Neoral** at the same dose. We describe our experience of 51 patients treated with **Neoral**--39 with rheumatoid

arthritis, six with psoriatic arthritis and the remainder with a variety of diseases, including Behcet's, systemic lupus erythematosus and juvenile chronic arthritis. All patients continued their other medication including non-steroidal anti-inflammatory drugs and analgesics. Five continued low dose prednisolone (average 7.5 mg per day) all patients were monitored for safety and efficacy throughout their treatment according to standard protocol. Five patients were enrolled in a study of efficacy and safety where the dose of \*\*\*cyclosporin\*\*\* was reduced to 2.5 mg/kg/day at the time of conversion, i.e. to **Neoral** 2.5 mg/kg/day; 19 patients were converted dose for dose, **cyclosporin A** dose range 2.5-4 mg/kg/day converted to \*\*\*Neoral\*\*\* dose range 2.5-4 mg/kg/day and 27 patients started \*\*\*Neoral\*\*\* de novo. We conclude that **cyclosporin** is a useful disease modifying anti-rheumatic agent, and our experience suggests that the new formulation, **Neoral**, has a similar safety and efficacy profile to the original preparation (**Sandimmun**). **Neoral** was relatively easy to manage and we noted a slight reduction in dose when compared to **Sandimmun**. With dose adjustments over 18 months the mean dose for patients with RA fell from 3.2 to 2.7 mg/kg/day and of the 27 patients starting \*\*\*Neoral\*\*\* de novo only seven required an increased dose above 2.5 mg/kg/day in order to establish efficacy.

CONTROLLED TERM: Adolescent  
 Adult  
 Anti-Inflammatory Agents: TU, therapeutic use  
 Antirheumatic Agents: AD, administration & dosage  
 Antirheumatic Agents: PK, pharmacokinetics  
 \*Antirheumatic Agents: TU, therapeutic use  
 Arthritis, Juvenile Rheumatoid: DT, drug therapy  
 Arthritis, Psoriatic: DT, drug therapy  
 Arthritis, Rheumatoid: DT, drug therapy  
 Behcet Syndrome: DT, drug therapy  
 Biological Availability  
 Cyclosporine: AD, administration & dosage  
 Cyclosporine: PK, pharmacokinetics  
 \*Cyclosporine: TU, therapeutic use  
 Dose-Response Relationship, Drug  
 Drug Therapy: EC, economics  
 Emulsions  
 Humans  
 Lupus Erythematosus, Systemic: DT, drug therapy  
 Middle Aged  
 Prednisolone: TU, therapeutic use  
 Questionnaires  
 \*Rheumatic Diseases: DT, drug therapy  
 Severity of Illness Index  
 CAS REGISTRY NO.: 50-24-8 (Prednisolone); 59865-13-3 (Cyclosporine)  
 CHEMICAL NAME: 0 (Anti-Inflammatory Agents); 0 (Antirheumatic Agents); 0 (Emulsions)

L139 ANSWER 12 OF 73 MEDLINE on STN  
 ACCESSION NUMBER: 1998209717 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 9550347  
 TITLE: Effect of topical **cyclosporin A** on Thygeson's superficial punctate keratitis.  
 AUTHOR: Del Castillo J M; Del Castillo J B; Garcia-Sanchez J  
 CORPORATE SOURCE: Instituto de Investigaciones Oftalmologicas Ramon Castroviejo, Madrid, Spain.  
 SOURCE: Documenta ophthalmologica. Advances in ophthalmology, (1996-1997) Vol. 93, No. 3, pp. 193-8.  
 Journal code: 0370667. ISSN: 0012-4486.  
 PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199806  
ENTRY DATE: Entered STN: 25 Jun 1998  
Last Updated on STN: 25 Jun 1998  
Entered Medline: 16 Jun 1998

ABSTRACT:

Thygeson's superficial punctate keratitis (Thygeson's SPK) is a distinct clinical entity, characterized by round conglomerates of discrete, granular, white-gray, fine intraepithelial dots without conjunctival involvement. The only effective treatment with regard to relieving symptoms and diminishing lesions has been topical corticosteroids, but their prolonged use can be associated with severe side-effects. The purpose of this study is to present the long-term results of the use of 2% topical **cyclosporin A** in olive oil in Thygeson's SPK. Eight patients diagnosed as having Thygeson's SPK were included. All the patients were treated with 2% **cyclosporin** dissolved in olive oil four times a day for three months, and two times a day for one month before withdrawing therapy. The follow-up period ranged from twelve to twenty-five months. The number of corneal lesions varied between 5 and 15 before treatment. After **cyclosporin** treatment, no corneal lesion was observed and the cornea remained clear after the follow-up period. In conclusion, 2% **cyclosporin** in olive oil is a safe alternative to corticosteroids in the treatment of Thygeson's SPK, and resulted in satisfactory control of the condition.

CONTROLLED TERM: Check Tags: Female; Male  
Administration, Topical  
Adolescent  
Adult  
\*Cornea: DE, drug effects  
Cornea: PA, pathology  
Cyclosporine: AD, administration & dosage  
\*Cyclosporine: TU, therapeutic use  
Drug Combinations  
Follow-Up Studies  
Humans  
Immunosuppressive Agents: AD, administration & dosage  
\*Immunosuppressive Agents: TU, therapeutic use  
\*Keratitis: DT, drug therapy  
Keratitis: ET, etiology  
Keratitis: PA, pathology  
Middle Aged  
Ophthalmic Solutions  
Plant Oils: AD, administration & dosage  
\*Plant Oils: TU, therapeutic use  
Treatment Outcome  
CAS REGISTRY NO.: 59865-13-3 (Cyclosporine); 8001-25-0 (olive oil)  
CHEMICAL NAME: 0 (Drug Combinations); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions); 0 (Plant Oils)

L139 ANSWER 13 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 94208262 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 8156785  
TITLE: Influence of topically applied **cyclosporine A** in olive oil on corneal epithelium permeability.  
AUTHOR: Benitez del Castillo J M; del Aguila C; Duran S; Hernandez J; Garcia Sanchez J  
CORPORATE SOURCE: Department of Ophthalmology, Hospital Universitario San Carlos, Universidad Complutense de Madrid, Spain.  
SOURCE: Cornea, (1994 Mar) Vol. 13, No. 2, pp. 136-40.

Journal code: 8216186. ISSN: 0277-3740.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199405  
ENTRY DATE: Entered STN: 26 May 1994  
Last Updated on STN: 6 Feb 1998  
Entered Medline: 19 May 1994

ABSTRACT:

The effect that topically administered **cyclosporine A** (CsA) dissolved in olive oil has on corneal epithelial permeability was determined by fluorophotometry. Twenty-six healthy volunteers, who had no ocular or general disease and were not receiving any topical or systemic treatments, were studied. A Fluorotron Master fluorophotometer was used. Measurements were taken before and 45 min after the instillation of 40 microliters of a 2% aqueous solution of sodium fluorescein without preservatives. Basal corneal epithelial permeability, as well as the permeability 24 h after the instillation of 2% CsA-olive oil and of the solvent alone, were calculated. Under sterile conditions, the **Sandimmun** oral solution (Sandoz, Basel, Switzerland) was used to prepare the topical 2% CsA. Immediately after the 2% CsA-olive oil or the solvent alone were instilled, the volunteers complained of itching for approximately 1 h and developed punctate keratopathy, which improved the next day. Epithelial permeability 24 h after instillation of 2% CsA-olive oil increased 7.03 times ( $p < 0.001$ ), and that of the solvent alone increased 6.68 times ( $p < 0.001$ ). No differences in corneal permeability were found between CsA-olive oil and the vehicle ( $p = 0.651$ ). We concluded that the olive oil used to dissolve CsA is responsible for the increased corneal epithelial permeability.

CONTROLLED TERM: Check Tags: Female; Male  
Administration, Topical  
Adult  
Cell Membrane Permeability: DE, drug effects  
\*Cornea: ME, metabolism  
Corneal Diseases: CI, chemically induced  
Cyclosporine: AE, adverse effects  
\*Cyclosporine: PD, pharmacology  
Emulsions  
Fluorescein  
Fluoresceins: PK, pharmacokinetics  
Fluorophotometry  
Humans  
Ophthalmic Solutions  
Plant Oils  
Pruritus: CI, chemically induced  
CAS REGISTRY NO.: 2321-07-5 (Fluorescein); 59865-13-3 (Cyclosporine)  
; 8001-25-0 (olive oil)  
CHEMICAL NAME: 0 (Emulsions); 0 (Fluoresceins); 0 (Ophthalmic Solutions);  
0 (Plant Oils)

L139 ANSWER 14 OF 73 MEDLINE on STN  
ACCESSION NUMBER: 89334669 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 2757551  
TITLE: Spontaneous canine keratoconjunctivitis sicca. A useful model for human keratoconjunctivitis sicca: treatment with **cyclosporine** eye drops.  
AUTHOR: Kaswan R L; Salisbury M A; Ward D A  
CORPORATE SOURCE: Department of Small Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens 30602.  
SOURCE: Archives of ophthalmology, (1989 Aug) Vol. 107, No. 8, pp.

1210-6.  
Journal code: 7706534. ISSN: 0003-9950.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 198909  
ENTRY DATE: Entered STN: 9 Mar 1990  
Last Updated on STN: 9 Mar 1990  
Entered Medline: 1 Sep 1989

ABSTRACT:

Thirty-six sequential cases of canine keratoconjunctivitis sicca (KCS) were treated with ophthalmic **cyclosporine**. The effects of topical **cyclosporine** were twofold: (1) **cyclosporine** increased tear production by 5 mm/min or greater in all cases of spontaneous KCS having an initial Schirmer's Tear Test value greater than 2 mm/min and in 59% of eyes with an initial Schirmer's Tear Test value of 0 to 2 mm/min, and (2) **cyclosporine** caused marked regression of chronic corneal neovascularization and granulation even in eyes in which lacrimation failed to improve. Additional benefits of topical **cyclosporine** were reduced mucopurulent conjunctivitis, rapid healing of nonhealing corneal ulcers, and reduced dependence on frequent topical treatments of KCS. Twelve normal beagles treated with topical **cyclosporine** also had a reversible increase in lacrimation compared with baseline or placebo control-treated dogs.

CONTROLLED TERM: Check Tags: Female; Male  
Animals  
Cornea: PA, pathology  
Cyclosporins: AD, administration & dosage  
\*Cyclosporins: TU, therapeutic use  
Disease Models, Animal  
\*Dog Diseases: DT, drug therapy  
Dog Diseases: PA, pathology  
Dogs  
Double-Blind Method  
\*Keratoconjunctivitis: VE, veterinary  
Keratoconjunctivitis Sicca: DT, drug therapy  
Keratoconjunctivitis Sicca: PA, pathology  
\*Keratoconjunctivitis Sicca: VE, veterinary  
Ophthalmic Solutions  
Plant Oils  
Tears: DE, drug effects  
Tears: SE, secretion  
Vehicles  
CAS REGISTRY NO.: 8001-25-0 (olive oil)  
CHEMICAL NAME: 0 (Cyclosporins); 0 (Ophthalmic Solutions); 0 (Plant Oils); 0 (Vehicles)

L139 ANSWER 15 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 3

ACCESSION NUMBER: 1990:113390 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199089062881; BA89:62881  
TITLE: THE EFFECT ON THE CORNEA OF VARIOUS VEHICLES FOR  
CYCLOSPORIN EYE DROPS.  
AUTHOR(S): ALBA R M JR [Reprint author]; KANAI A; TAKANO T; KOBAYASHI  
C; NAKAJIMA A; KURIHARA K; FUKAMI M  
CORPORATE SOURCE: DEP OPHTHALMOL, JUNTENDO UNIV SCH MED, 3-1-3 HONGO,  
BUNKYO-KU, TOKYO 113, JAPAN

SOURCE: Folia Ophthalmologica Japonica, (1989) Vol. 40, No. 5, pp. 902-908.

CODEN: NGKYA3. ISSN: 0015-5667.

DOCUMENT TYPE: Article

FILE SEGMENT: BA

LANGUAGE: ENGLISH

ENTRY DATE: Entered STN: 21 Feb 1990

Last Updated on STN: 22 Feb 1990

ABSTRACT: We tested several solvents, possible vehicles for Cyclosporin, (CYA) as to which had the least corneal toxicity. They were: peanut \*\*\*oil\*\*\*, palm oil, polyoxyethylene castor oil, medium chain-length triglyceride emulsion (MCT) and alpha cyclo-dextrin ( $\alpha$ -CD). The concentration of CYA in each vehicle was: 1% in peanut \*\*\*oil\*\*\*, palm oil and MCT; 0.1% in polyoxyethylene castor \*\*\*oil\*\*\* and 0.08% in  $\alpha$ -CD. The drugs and normal saline, which served as control, were instilled to rat corneas at frequencies of 10 + (every 30 min.) and 5+. Light microscopy revealed that in the MCT,  $\alpha$ -CD and peanut oil groups, corneal thickness approximated that in the controls. In the next phase, done on rabbit corneas, we instilled MCT (with and without CYA),  $\alpha$ -CD and peanut oil 10+ (every 30 min.). Normal saline was applied to the control eye. The Draize test, ultrasonic pachymetry, light and electron microscopic examination indicated that, compared to the other vehicles,  $\alpha$ -CD exhibited significant corneal toxicity was evidenced by edema, diminution of microvilli on the epithelium and epithelial craters. Radioimmunoassay of CYA levels in the cornea and aq. humor indicated that  $\alpha$ -CD afforded the greatest CYA penetration of the cornea. We then tested 4 different concentrations of  $\alpha$ -CD to determine the least toxic concentration. The concentrations were: 80, 40, 20 and 10 mg/ml. of  $\alpha$ -CD combined with 0.75, 0.25, 0.09 and 0.03 mg./ml. of CYA. They were applied to rabbit corneas 4+ (every 2 hrs.) Histological and RIA studies indicate that 40.0 mg/ml  $\alpha$ -CD with 0.25 mg./ml. CYA is an acceptable concentration.

CONCEPT CODE: Microscopy - Histology and histochemistry 01056  
Cytology - Human 02508  
Radiation biology - Radiation and isotope techniques 06504  
Biochemistry studies - General 10060  
Biochemistry studies - Proteins, peptides and amino acids 10064  
Biochemistry studies - Lipids 10066  
Anatomy and Histology - Microscopic and ultramicroscopic anatomy 11108  
Pathology - Therapy 12512  
Sense organs - General and methods 20001  
Sense organs - Pathology 20006  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Sense organs, associated structures and functions 22031  
Routes of immunization, infection and therapy 22100  
Immunology - General and methods 34502  
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts  
Immune System (Chemical Coordination and Homeostasis);  
Morphology; Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Miscellaneous Descriptors  
RABBIT IMMUNOSUPPRESSANT-DRUG PEANUT OIL PALM  
OIL ALPHA CYCLODEXTRIN MEDIUM CHAIN-LENGTH  
TRIGLYCERIDE EMULSION ULTRASONIC PACHYMETRY



DRAIZE TEST LIGHT MICROSCOPY ELECTRON MICROSCOPY  
RADIOIMMUNOASSAY

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 59865-13-3Q (CYCLOSPORIN)  
79217-60-0Q (CYCLOSPORIN)  
10016-20-3 (ALPHA-CYCLODEXTRIN)

L139 ANSWER 16 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

ACCESSION NUMBER: 2004:38676 BIOSIS Full-text  
DOCUMENT NUMBER: PREV200400039347  
TITLE: Method and composition for dry **eye** treatment.  
AUTHOR(S): Benita, Simon [Inventor, Reprint Author]; Lambert, Gregory  
[Inventor]  
CORPORATE SOURCE: Mevaseret Zion, Israel  
ASSIGNEE: Yissum Research Development, Jerusalem, Israel;  
Company of the Hebrew University of Jerusalem Novagali  
S.A.S., Evry, France  
PATENT INFORMATION: US 6656460 20031202  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Dec 2 2003) Vol. 1277, No. 1.  
<http://www.uspto.gov/web/menu/patdata.html>. e-file.  
ISSN: 0098-1133 (ISSN print).

DOCUMENT TYPE: Patent  
LANGUAGE: English  
ENTRY DATE: Entered STN: 7 Jan 2004  
Last Updated on STN: 7 Jan 2004

ABSTRACT: A method and composition for treating a dry **eye** condition by  
topically applying to the **eye** surfaces an **emulsion** forming  
a tear film that acts to lubricate the **eye** and to inhibit evaporation  
therefrom. The **emulsion** is constituted by water in which is  
dispersed a mixture that includes a phospholipid, a non-polar **oil**, a  
non-toxic **emulsifying** agent and a polar lipid that imparts a net  
positive charge to the film that is distributed throughout the film, causing  
the film to be electrostatically attracted to the anionic surface of the  
\*\*\*eye\*\*\* whereby the film adheres thereto and cannot be washed away.  
Includable in the mixture is a non-soluble therapeutic agent, such as  
\*\*\*cyclosporin\*\*\* which is effective against an **eye** disease and is  
delivered to the **eye** by the film.

NAT. PATENT. CLASSIF.: 424780400

CONCEPT CODE: Pathology - Therapy 12512  
Sense organs - Pathology 20006  
Pharmacology - General 22002  
Pharmacology - Sense organs, associated structures and  
functions 22031

INDEX TERMS: Major Concepts  
Methods and Techniques; Pharmacology

INDEX TERMS: Diseases  
dry **eye**: **eye** disease, drug therapy  
Dry **Eye** Syndromes (MeSH)

INDEX TERMS: Chemicals & Biochemicals  
dry **eye** treatment composition: ophthalmic-drug

INDEX TERMS: Methods & Equipment  
dry **eye** treatment method: clinical techniques,



US005474979A

# United States Patent [19]

Ding et al.

[11] Patent Number: **5,474,979**

[45] Date of Patent: **Dec. 12, 1995**

[54] **NONIRRITATING EMULSIONS FOR SENSITIVE TISSUE**

[75] Inventors: **Shulin Ding; Walter L. Tien**, both of Irvine; **Orest Olejnik**, Trabuco Canyon, all of Calif.

[73] Assignee: **Allergan, Inc.**, Irvine, Calif.

[21] Appl. No.: **243,279**

[22] Filed: **May 17, 1994**

[51] Int. Cl.<sup>6</sup> ..... **A61K 38/13; A61K 47/34**

[52] U.S. Cl. .... **514/11; 514/785; 514/786; 514/912; 514/941; 514/943; 514/975**

[58] Field of Search ..... **530/317, 321; 514/9, 11, 785, 786, 912, 913, 914, 915, 941, 943, 975, 178, 179, 180, 181, 420, 784; A61K 9/107, 47/14**

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

4,347,238 8/1982 Hollingsbee ..... 514/179

4,839,342	6/1989	Kaswan .....	514/11
4,990,337	2/1991	Kurihara et al. ....	424/427
4,996,193	2/1991	Hewitt et al. ....	514/11
5,051,402	9/1991	Kurihara et al. ....	514/11
5,364,632	11/1994	Benita et al. ....	514/943

*Primary Examiner*—Jeffrey E. Russel  
*Attorney, Agent, or Firm*—Walter A. Hackler

[57] **ABSTRACT**

A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixture with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporin A and the higher fatty acid glyceride may be castor oil. Composition has been found to be of a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues. In addition, the composition has stability for up to nine months without crystallization of cyclosporin.

**8 Claims, No Drawings**

## NONIRRITATING EMULSIONS FOR SENSITIVE TISSUE

The present invention generally relates to novel pharmaceutical compositions incorporating chemicals which are poorly soluble in water and is more particularly related to a novel ophthalmic emulsion including cyclosporin in admixture with castor oil and polysorbate 80 with high comfort level and low irritation potential.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. In addition, as set forth in U.S. Pat. No. 4,839,342, cyclosporin (sometimes referred to in the literature as "cyclosporine") has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.

As hereinabove noted, cyclosporin comprises a group of cyclic oligopeptides and the major component thereof is cyclosporin A ( $C_{62}H_{111}N_{11}O_{12}$ ) which has been identified along with several other minor metabolites, cyclosporin B through I. 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 residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

It should be appreciated that reference to the term "cyclosporin" or "cyclosporins" is used throughout the present specification in order to designate the cyclosporin component in the composition of the present invention.

However, this specific reference is intended to include any individual member of the cyclosporin group as well as admixtures of two or more individual cyclosporins, whether natural or synthetic.

The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.

Unfortunately, the solubility of cyclosporin in water is extremely low and as elaborated in U.S. Pat. No. 5,051,402, it has been considered not merely difficult but practically impossible to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium.

As reported, the solubility of cyclosporin in water is between about 20  $\mu\text{g}/\text{ml}$  to 30  $\mu\text{g}/\text{ml}$  for cyclosporin A. Hence, heretofore prepared formulations incorporating cyclosporin have been prepared as oily solutions containing ethanol. However, these preparations limit the bioavailability to oral preparations and this is believed to be due to the separation of cyclosporin as a solid immediately after it comes into contact with water, such as in the mouth or eye of a patient.

In the case of injectable preparations of cyclosporin, they first must be diluted with physiological saline before intravenous administration but this is likely to result in the precipitation of cyclosporin and therefore may be considered undesirable for intravenous administration.

Surface active agents such as polyoxyethylated castor oil have been utilized as solubilizers to inject preparations in order to prevent cyclosporin from separating. However, this also may give rise to safety problems (see U.S. Pat. No. 5,051,402).

The practical usefulness of cyclosporin would be greatly enhanced if administration thereof could be effective; for example, cyclosporin's effectiveness in the treatment of ocular symptoms of Behcet's Syndrome. However, if it is

administered orally for the treatment of these symptoms, the accompanying side effects due to systemic circulation may cause adverse reactions such as hypertrichosis or renal dysfunction.

On the other hand, if oily preparations containing cyclosporin are applied directly to the eyes, irritation or a clouding of visual field may result. This plus the difficulty in formulating cyclosporin limits its use in formulations that would be useful during keratoplasty as well in the treatment of herpetic keratitis and spring catarrh.

Heretofore, as for example in U.S. Pat. No. 5,051,402, attempts have been made to dissolve sufficient cyclosporin in an aqueous solvent system so as to reach an effective concentration for treatment. Importantly, this solvent system does not contain any surface active agent such as polyoxyethylated castor oil.

Conceptually, the purpose of dissolving the cyclosporin in an aqueous solvent system is to enable contact with body fluids which would merely constitute dilution of the aqueous solvent system which hopefully would eliminate the immediate precipitation of cyclosporin when contacted with the water content of the body fluids.

For direct use in the eye, cyclosporin has been formulated with a number of pharmaceutically acceptable excipients, for example, animal oil, vegetable oil, an appropriate organic or aqueous solvent, an artificial tear solution, a natural or synthetic polymer or an appropriate membrane.

Specific examples of these pharmaceutically acceptable excipients, which may be used solely or in combination, are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, chremophor, liposomes, or liposome-like products or a silicone fluid, among others.

In summary, a great deal of effort has been expended in order to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium or cyclosporin prepared as an oily solution. However, successful formulations have yet to be accomplished as evidenced by the lack of commercial products.

As hereinabove noted, it has been reported that cyclosporin has demonstrated some solubility in oily preparations containing higher fatty acid glycerides such as olive oil, peanut oil, and/or castor oil. These formulations frequently produce an unpleasant sensation when applied to the eye because of stimulation or the viscousness which is characteristic of these oils.

Another drawback of these formulations is that they contain a high concentration of oils, and oils exacerbate the symptoms of certain ocular surface diseases such as dry eyes, indicated by cyclosporin. Therefore, these oily formulations may not be clinically acceptable. Additionally, these formulations often suffer from physical instability due to cyclosporin's propensity to undergo conformational change and crystallize out. The crystallization problem has been noticed in formulations containing corn oil or medium chain triglycerides. Lastly, these formulations often have a low thermodynamic activity (degree of saturation) of cyclosporin which leads to a poorer drug bioavailability.

It may be possible to minimize the problems related to unpleasant sensation and syndrome exacerbation by reducing the oil content and dispersing the oil phase in water into an emulsion. However, it is not an easy task to formulate an ophthalmic emulsion because one indispensable class of ingredients in an emulsion system is emulsifiers, and the majority of emulsifiers is highly irritating to the eyes.

The present invention is directed to an emulsion system which utilizes higher fatty acid glycerides but in combination with polysorbate 80 which results in an emulsion with

a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues.

### SUMMARY OF THE INVENTION

In accordance with the present invention, a nonirritating pharmaceutical composition with high comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues comprises cyclosporin in admixture with an emulsifying amount of a higher fatty acid glycerol and polysorbate 80. More particularly, the composition may comprise cyclosporin A and the higher fatty acid glyceride may comprise castor oil.

Preferably, the weight ratio of the castor oil to the polysorbate 80 is between about 0.3 to about 30 and a weight ratio of the cyclosporin to castor oil is below 0.16. More preferably, the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5, and the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.

When cyclosporin is dissolved in the oil phase in accordance with the present invention, the emulsion is found to be physically stable upon long term storage. No crystallization of cyclosporin was noticed after nine months at room temperature. Moreover, the cyclosporin emulsion is formulated in such a way that the drug has reasonably high thermodynamic activity, yet without the crystallization problem.

### DETAILED DESCRIPTION

As hereinabove noted, cyclosporin is available as a mixture in which the principal ingredient is cyclosporin A with significant, but smaller, quantities of other cyclosporins such as cyclosporin B through I. However, as also hereinabove noted, the present invention may be applied to either a pure cyclosporin or to a mixture of individual cyclosporins.

The discovery on which the present invention is founded relates to a combination of a higher fatty acid glyceride and an emulsifier and dispersing agent, polysorbate 80. The selection of these components could not have been anticipated on the basis of conventional thinking.

For example, although it is well-known that cyclosporin may be used in combination with castor oil, this combination is irritating to sensitive tissues such as the eye. Thus, conventional teaching in the art is away from a formulation which utilizes a higher fatty acid glyceride, such as castor oil, and cyclosporin.

Stated another way, there is no way of deducing that the use of an emulsifier and dispersing agent such as polysorbate 80 will reduce the irritation potential of an emulsion utilizing castor oil. There are no examples of polysorbate in combination with castor oil which, when admixed to cyclosporin, produces an emulsion with a high comfort level and low irritation potential suitable for the delivery of medication to sensitive areas such as ocular tissues.

The present invention achieves a stable solution state of cyclosporin. This stable solution state is another important performance characteristic differentiating the present invention from the conventional oil systems. Cyclosporin is notorious for its tendency to precipitate out in conventional oil systems in which it is fully dissolved initially.

In accordance with the present invention, the emulsions can be further stabilized using a polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen®.

Pemulen® is a registered trademark of B. F. Goodrich for polymeric emulsifiers and commercially available from B. F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers. They are high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol. They contain not less than 52.0 percent and not more than 62.0 percent of carboxylic acid groups. The viscosity of a neutralized 1.0 percent aqueous dispersion is between 9,500 and 26,500 centipoises.

In addition, the tonicity of the emulsions can be further adjusted using glycerine, mannitol, or sorbitol if desired. The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide to a near physiological pH level and while buffering agents are not required, suitable buffers may include phosphates, citrates, acetates and borates.

While the preferable medications in accordance with the present invention include cyclosporin, other chemicals which are poorly soluble in water such as indomethacin and steroids such as androgens, prednisolone, prednisolone acetate, fluorometholone, and dexamethasones, may be emulsified with castor oil and polysorbate 80 resulting in a composition with similar low irritation potential.

The invention is further illustrated by the following examples with all parts and percentages expressed by weight. The cyclosporin used in the examples was supplied by Sandoz.

Example 1					
	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

Example 2				
	A	B	C	D
Castor oil	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs
Purified water	qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

Example 3		
	A	
Castor oil	2.50%	
Polysorbate 80	0.75%	
Carbomer 1382	0.05%	
Glycerine	2.20%	
NaOH	qs	
Purified water	qs	
pH	7.2-7.6	

Example 4	
	A
Castor oil	5.00%

-continued

Polysorbate 80	0.75%
Carbomer 981	0.05%
Glycerin	2.20%
NaOH	qs
Purified water	qs
pH	7.2-7.6

The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome with Examples 2, 3 and 4 without the active ingredient cyclosporin utilized to determine the toxicity of the emulsified components.

The formulations in Examples 1-4 were applied to rabbit eyes eight times a day for seven days and were found to cause only slight to mild discomfort and slight hyperemia in the rabbit eyes. Slit lamp examination revealed no changes in the surface tissue. In addition, the cyclosporin containing castor oil emulsion, as hereinabove set forth in Examples 1A-1D, was also tested for ocular bioavailability in rabbits; and the therapeutic level of cyclosporin was found in the tissues of interest after dosage. This substantiates that cyclosporin in an ophthalmic delivery system is useful for treating dry eye as set forth in U.S. Pat. No. 4,839,342.

In addition, no difference in toxicity was found between formulations with cyclosporin (Examples 1A-1D) and formulations without cyclosporin (Examples 2-4).

The formulations set forth in Examples 1-4 were found to be physically stable upon long term storage. With regard to formulations 1A-1D, no crystallization of cyclosporin was noticed after nine months at room temperature.

Further, other higher fatty acid glycerides such as olive oil, peanut oil and the like may also be utilized with the polysorbate 80 with similar results regarding biotoxicity.

Although there has been hereinabove described a particular pharmaceutical composition in the form of a nonirritating emulsion for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements, which may occur to those skilled in the art, should be considered to be within the scope of the present

invention as defined in the appended claims.

What is claimed is:

1. A pharmaceutical composition comprising a nonirritating emulsion of at least one cyclosporin in admixture with a higher fatty acid glyceride, polysorbate 80 and an emulsion stabilizing amount of Pemulen in water suitable for topical application to ocular tissue.

2. The pharmaceutical composition according to claim 1 wherein the cyclosporin comprises cyclosporin A.

3. The pharmaceutical composition according to claim 2 wherein the weight ratio of the higher fatty acid glyceride to the polysorbate 80 is between about 0.3 and about 30.

4. The pharmaceutical composition according to claim 3 wherein the higher fatty acid glyceride comprises castor oil and the weight ratio of cyclosporin to castor oil is below about 0.16.

5. The composition according to claim 1 wherein the higher fatty acid glyceride and polysorbate 80 are present in amounts sufficient to prevent crystallization of cyclosporin for a period of up to about nine months.

6. A pharmaceutical emulsion comprising of cyclosporin A, castor oil, Pemulen, glycerine, polysorbate 80 water in amounts sufficient to prevent crystallization of cyclosporin A for a period of up to about nine months, said pharmaceutical emulsion being suitable for topical application to ocular tissue.

7. The pharmaceutical emulsion according to claim 6 wherein the cyclosporin A is present in an amount of between about 0.05 to and about 0.40%, by weight, the castor oil is present in an amount of between about 0.625%, by weight, and about 5.0%, by weight, the polysorbate 80 is present in an amount of about 1.0%, by weight, the Pemulen is present in an amount of about 0.05%, by weight, and the glycerine is present in an amount of about 2.2%, by weight.

8. A pharmaceutical emulsion consisting of between about 0.05% and about 0.40%, by weight, cyclosporin A, between about 0.625% and about 5.0%, by weight, castor oil, about 1.0%, by weight, polysorbate 80, about 0.05%, by weight, Pemulen and about 2.2%, by weight, glycerine in water with a pH of between about 7.2 and 7.6 suitable for topical application to ocular tissue.

\* \* \* \* \*

0.05 cycl.  
1.25% cast oil

10/927, 857

D-3111

29

WHAT IS CLAIMED IS:

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

5 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.

therapeutic and prophylactic techniques

L139 ANSWER 17 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

ACCESSION NUMBER: 2004:98054 BIOSIS Full-text  
DOCUMENT NUMBER: PREV200400099351  
TITLE: **Cyclosporine A** delivery to the  
**eye**: A pharmaceutical challenge.  
AUTHOR(S): Lallemand, F.; Felt-Baeyens, O.; Besseghir, K.;  
Behar-Cohen, F.; Gurny, R. [Reprint Author]  
CORPORATE SOURCE: School of Pharmacy, University of Geneva, 30, quai E.  
Ansermet, CH-1211, Geneva, 4, Switzerland  
robert.gurny@pharm.unige.ch  
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics,  
(November 2003) Vol. 56, No. 3, pp. 307-318. print.  
ISSN: 0939-6411 (ISSN print).  
DOCUMENT TYPE: Article  
General Review; (Literature Review)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 18 Feb 2004  
Last Updated on STN: 18 Feb 2004

ABSTRACT: Systemic administration of **cyclosporine A** (CsA) is commonly used in the treatment of local ophthalmic conditions involving cytokines, such as corneal graft rejection, autoimmune uveitis and dry **\*\*\*eye\*\*\*** syndrome. Local administration is expected to avoid the various side effects associated with systemic delivery. However, the currently available systems using oils to deliver CsA topically are poorly tolerated and provide a low bioavailability. These difficulties may be overcome through formulations aimed at improving CsA water solubility (e.g. cyclodextrins), or those designed to facilitate tissue drug penetration using penetration enhancers. The use of colloidal carriers (micelles, **\*\*\*emulsions\*\*\***, liposomes and nanoparticles) as well as the approach using hydrosoluble prodrugs of CsA have shown promising results. Solid devices such as shields and particles of collagen have been investigated to enhance retention time on the **eye** surface. Some of these topical formulations have shown efficacy in the treatment of extraocular diseases but were inefficient at reaching intraocular targets. Microspheres, implants and liposomes have been developed to be directly administered subconjunctivally or intravitreally in order to enhance CsA concentration in the vitreous. Although progress has been made, there is still room for improvement in CsA ocular application, as none of these formulations is ideal.

CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids  
10064  
Pathology - Therapy 12512  
Sense organs - Physiology and biochemistry 20004  
Pharmacology - General 22002  
Pharmacology - Immunological processes and allergy 22018  
INDEX TERMS: Major Concepts  
Pharmacology; Sense Organs (Sensory Reception)  
INDEX TERMS: Parts, Structures, & Systems of Organisms  
**eye**: sensory system; vitreous: sensory system  
INDEX TERMS: Chemicals & Biochemicals  
**cyclosporine A**: immunologic-drug,  
immunosuppressant-drug, ocular delivery, systemic  
administration, topical administration, water solubility  
INDEX TERMS: Methods & Equipment  
**emulsions**: drug delivery device; implants:  
drug delivery device; liposomes: drug delivery device;  
micelles: drug delivery device; microspheres: drug  
delivery device; nanoparticles: drug delivery device

ORGANISM: Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rat (common): animal model  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates,  
Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 59865-13-3 (cyclosporine A)

L139 ANSWER 18 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
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ACCESSION NUMBER: 2002:182305 BIOSIS Full-text  
DOCUMENT NUMBER: PREV200200182305  
TITLE: **Cyclosporine A** formulation affects its  
ocular distribution in rabbits.  
AUTHOR(S): Kuwano, Mitsuaki [Reprint author]; Ibuki, Hajime; Morikawa,  
Nobuo; Ota, Atsutoshi; Kawashima, Yoichi  
CORPORATE SOURCE: Ophthalmic Research Division, Santen Pharmaceutical Co.,  
LTD., Ikoma-shi, Nara, 630-0101, Japan  
kuwanom@santen.co.jp  
SOURCE: Pharmaceutical Research (New York), (January, 2002) Vol.  
19, No. 1, pp. 108-111. print.  
CODEN: PHREEB. ISSN: 0724-8741.

DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 6 Mar 2002  
Last Updated on STN: 6 Mar 2002

CONCEPT CODE: Sense organs - Physiology and biochemistry 20004  
Pathology - Therapy 12512  
Pharmacology - General 22002  
Pharmacology - Drug metabolism and metabolic stimulators  
22003  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Sense organs, associated structures and  
functions 22031

INDEX TERMS: Major Concepts  
Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Parts, Structures, & Systems of Organisms  
**eye**: sensory system

INDEX TERMS: Chemicals & Biochemicals  
HCO-60-**cyclosporine A**:  
immunologic-drug, immunosuppressant-drug,  
ophthalmic-drug; MYS-40-**cyclosporine A**  
: immunologic-drug, immunosuppressant-drug,  
ophthalmic-drug; Tween 80-**cyclosporine**  
**A**: immunologic-drug, immunosuppressant-drug,  
ophthalmic-drug; nonionic surfactants; **oil-**  
**cyclosporine A**: immunologic-drug,  
immunosuppressant-drug, ophthalmic-drug; **oil**  
/**water emulsion-cyclosporine**  
**A**: immunologic-drug, immunosuppressant-drug,  
ophthalmic-drug

INDEX TERMS: Methods & Equipment  
high performance liquid chromatography: liquid  
chromatography, measurement method; topical application:  
drug administration method

INDEX TERMS: Miscellaneous Descriptors  
ocular distribution; pharmacokinetics

ORGANISM: Classifier  
 Leporidae 86040  
 Super Taxa  
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 rabbit: animal model, breed-Japanese white  
 Taxa Notes  
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
 Vertebrates, Nonhuman Mammals, Vertebrates

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ACCESSION NUMBER: 1998:104244 BIOSIS Full-text  
 DOCUMENT NUMBER: PREV199800104244  
 TITLE: **Cyclosporine** ophthalmic O/W **emulsion**:  
 Formulation and **emulsion** characterization.  
 AUTHOR(S): Ding, Shulin; Olejnik, Orest  
 CORPORATE SOURCE: Pharmaceutical Sci., Research and Development, Allergan  
 Inc., Irvine, CA 92612, USA  
 SOURCE: Pharmaceutical Research (New York), (Nov., 1997) Vol. 14,  
 No. 11 SUPPL., pp. S41. print.  
 Meeting Info.: Annual Meeting of the American Association of  
 Pharmaceutical Scientists. Boston, Massachusetts, USA.  
 November 2-6, 1997. American Association of Pharmaceutical  
 Scientists.  
 CODEN: PHREEB. ISSN: 0724-8741.

DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)

LANGUAGE: English  
 ENTRY DATE: Entered STN: 3 Mar 1998  
 Last Updated on STN: 3 Mar 1998

CONCEPT CODE: Pharmacology - General 22002  
 Biochemistry studies - General 10060  
 Sense organs - General and methods 20001  
 Routes of immunization, infection and therapy 22100  
 General biology - Symposia, transactions and proceedings  
 00520

INDEX TERMS: Major Concepts  
 Pharmacology

INDEX TERMS: Chemicals & Biochemicals  
**cyclosporine**: ophthalmic-drug, **eye**  
 drop, formulation, ophthalmic oil-in-water  
**emulsion**, topical use

INDEX TERMS: Miscellaneous Descriptors  
 Meeting Abstract; Meeting Poster

ORGANISM: Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates,  
 Vertebrates

REGISTRY NUMBER: 59865-13-3Q (**cyclosporine**)  
 63798-73-2Q (**cyclosporine**)

L139 ANSWER 20 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
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ACCESSION NUMBER: 1997:77192 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199799383895  
TITLE: Tissue concentration of nanoencapsulated radio-labelled  
**cyclosporin** following peroral delivery in mice or  
ophthalmic application in rabbits.  
AUTHOR(S): Bonduelle, Sylvie; Carrier, Michel; Pimienta, Clara;  
Benoit, Jean-Pierre; Lenaerts, Vincent [Reprint author]  
CORPORATE SOURCE: Lab. Inc., 140 rue Blainville Est., Sainte-Therese, Quebec  
J7E 1M5, Canada  
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics,  
(1996) Vol. 42, No. 6, pp. 313-319.  
ISSN: 0939-6411.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 26 Feb 1997  
Last Updated on STN: 26 Feb 1997

ABSTRACT: Cold and tritiated **cyclosporin A** was entrapped into polyisohexylcyanoacrylate nanocapsules dispersed in an aqueous vehicle. This preparation was then instilled in the **eyes** of rabbits. After several time intervals post-dose, the animals were sacrificed and their **\*\*\*eyes\*\*\*** dissected. Radioactivity was determined in the different tissues. Concentrations superior to the therapeutic level were noted for over 48 h in the cornea, and 24 h in the posterior and anterior sclera. In the retina with choroid and in the anterior uvea, concentrations peaked at 1 and 6 h post-dose respectively. A secondary increase of the tissue concentration was then observed from 12 h post-dose on, with levels above the therapeutic threshold being observed at 24 h post-dose. The formulation was well tolerated, no clinical sign of irritation was noted. Thus nanocapsules may be an interesting alternative to the olive oil solution or ointments tested so far for the delivery of **cyclosporin A** to the **eye**. In addition to being safely applied locally, they maintain therapeutic levels in several tissues for longer time periods than the solution in olive oil and allow therapeutic concentrations to be reached in the anterior uvea and retina with choroid, which has not been observed with the olive oil solution. The same type of formulation was administered perorally to fasted mice and compared to a commercial **emulsion** and a control **\*\*\*emulsion\*\*\*** (same preparation as nanocapsules without polymeric wall). As compared to the **emulsions**, nanoencapsulated **cyclosporin** had an increased bioavailability (blood AUC = 20500  $\mu\text{-g h ml}^{-1}$  for nanocapsules vs. 1650 and 1300  $\mu\text{-g h ml}^{-1}$  for the **emulsions**), a slower clearance from the blood and a reduced uptake by organs rich in reticuloendothelial cells (liver AUC = 22% of blood AUC for nanocapsules vs. 189% and 311% for the **\*\*\*emulsions\*\*\***). Concentration in the kidneys was lower with nanocapsules (kidneys AUC 9% of blood AUC for nanocapsules vs. 34% and 92% for the **\*\*\*emulsions\*\*\***), indicating that nanocapsules, in addition to allowing an increased bioavailability, also bear some promise at reducing the nephrotoxic adverse reactions of **cyclosporin A**.

CONCEPT CODE: Pharmacology - Drug metabolism and metabolic stimulators 22003  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Sense organs, associated structures and functions 22031  
Routes of immunization, infection and therapy 22100  
INDEX TERMS: Major Concepts  
Pharmacology  
INDEX TERMS: Chemicals & Biochemicals  
**CYCLOSPORIN**  
INDEX TERMS: Miscellaneous Descriptors  
BIOAVAILABILITY; IMMUNOSUPPRESSANT-DRUG;  
NANOENCAPSULATED RADIOLABELLED **CYCLOSPORIN**;

NEW ZEALAND WHITE RABBIT; NMRI MOUSE; OPHTHALMIC  
APPLICATION; OPHTHALMIC-DRUG; PERORAL DELIVERY;  
PHARMACOKINETICS; PHARMACOLOGY; TISSUE CONCENTRATION

ORGANISM: Classifier  
Leporidae 86040  
Super Taxa  
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
Leporidae  
Taxa Notes  
Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM: Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
Muridae  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates,  
Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 59865-13-3Q (CYCLOSPORIN)  
79217-60-0Q (CYCLOSPORIN)

L139 ANSWER 21 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

ACCESSION NUMBER: 1997:161965 BIOSIS Full-text  
DOCUMENT NUMBER: PREV199799461168  
TITLE: Tissue concentration of nanoencapsulated radio-labelled  
**cyclosporin** following peroral delivery in mice or  
ophthalmic application in rabbits.

AUTHOR(S): Bonduelle, Sylvie; Carrier, Michel; Pimienta, Clara;  
Benoit, Jean-Pierre; Lenaerts, Vincent [Reprint author]

CORPORATE SOURCE: Labopharm Inc., 140 rue Blainville Est, Sainte-Therese, PQ  
J7E 1M5, Canada

SOURCE: European Journal of Pharmaceutics and Biopharmaceutics,  
(1996) Vol. 42, No. 5, pp. 313-319.  
ISSN: 0939-6411.

DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 15 Apr 1997  
Last Updated on STN: 15 Apr 1997

ABSTRACT: Cold and tritiated **cyclosporin A** was entrapped  
into polyisohexylcyanoacrylate nanocapsules dispersed in an aqueous vehicle.  
This preparation was then instilled in the **eyes** of rabbits. After  
several time intervals post-dose, the animals were sacrificed and their  
**\*\*\*eyes\*\*\*** dissected. Radioactivity was determined in the different tissues.  
Concentrations superior to the therapeutic level were noted for over 48 h in  
the cornea, and 24 h in the posterior and anterior sclera. In the retina with  
choroid and in the anterior uvea, concentrations peaked at 1 and 6 h post-dose  
respectively. A secondary increase of the tissue concentration was then  
observed from 12 h post-dose on, with levels above the therapeutic threshold  
being observed at 24 h post-dose. The formulation was well tolerated, no  
clinical sign of irritation was noted. Thus nanocapsules may be an interesting  
alternative to the olive oil solution or ointments tested so far for  
the delivery of **cyclosporin A** to the **eye**. In  
addition to being safely applied locally, they maintain therapeutic levels in  
several tissues for longer time periods than the solution in olive oil  
and allow therapeutic concentrations to be reached in the anterior uvea and  
retina with choroid, which has not been observed with the olive oil

solution. The same type of formulation was administered perorally to fasted mice and compared to a commercial **emulsion** and a control **\*\*\*emulsion\*\*\*** (same preparation as nanocapsules without polymeric wall). As compared to the **emulsions**, nanoencapsulated **cyclosporin** had an increased bioavailability (blood AUC = 20500  $\mu\text{-g h ml}^{-1}$  for nanocapsules vs. 1650 and 1300  $\mu\text{-g h ml}^{-1}$  for the **emulsions**), a slower clearance from the blood and a reduced uptake by organs rich in reticuloendothelial cells (liver AUC = 22% of blood AUC for nanocapsules vs. 189% and 311% for the **\*\*\*emulsions\*\*\*** ). Concentration in the kidneys was lower with nanocapsules (kidneys AUC = 9% of blood AUC for nanocapsules vs. 34% and 92% for the **\*\*\*emulsions\*\*\*** ), indicating that nanocapsules, in addition to allowing an increased bioavailability, also bear some promise at reducing the nephrotoxic adverse reactions of **cyclosporin A**.

CONCEPT CODE: Pharmacology - Drug metabolism and metabolic stimulators 22003  
Pharmacology - Immunological processes and allergy 22018  
Pharmacology - Sense organs, associated structures and functions 22031  
Routes of immunization, infection and therapy 22100

INDEX TERMS: Major Concepts

Pharmacology

INDEX TERMS: Chemicals & Biochemicals

**CYCLOSPORIN**

INDEX TERMS: Miscellaneous Descriptors

BIOAVAILABILITY; IMMUNOSUPPRESSANT-DRUG;  
NANOENCAPSULATED RADIOLABELLED **CYCLOSPORIN**;  
OPHTHALMIC APPLICATION; OPHTHALMIC-DRUG; PERORAL  
DELIVERY; PHARMACEUTICAL FORMULATION; PHARMACOKINETICS;  
PHARMACOLOGY; TISSUE CONCENTRATION

ORGANISM:

Classifier

Leporidae 86040

Super Taxa

Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

rabbit

Taxa Notes

Animals, Chordates, Lagomorphs, Mammals, Nonhuman  
Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM:

Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

mouse

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates,  
Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER:

59865-13-3Q (**CYCLOSPORIN**)

79217-60-0Q (**CYCLOSPORIN**)

L139 ANSWER 22 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004467671 EMBASE Full-text

TITLE: The economic burden of dry eye: A conceptual framework and preliminary assessment.

AUTHOR: Reddy P.; Grad O.; Rajagopalan K.

CORPORATE SOURCE: P. Reddy, Abt Associates Inc., 55 Wheeler Street,



Cambridge, MA 02138, United States.

prabashni\_reddy@abtassoc.com

SOURCE: Cornea, (2004) Vol. 23, No. 8, pp. 751-761. .

Refs: 84

ISSN: 0277-3740 CODEN: CORNDB .

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 012 Ophthalmology  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 19 Nov 2004

Last Updated on STN: 19 Nov 2004

ABSTRACT: Purpose: To develop a conceptual framework for analyzing the economic burden of dry eye and a preliminary assessment of key factors that contribute to that burden. Methods: The MEDLINE database was searched from 1966 to May 2003 combining the term "dry eye" with various economic terms. In addition, individual interviews with a panel of clinicians were conducted to provide additional insight on resource use. Results: Direct resource utilization among dry eye sufferers includes healthcare professional visits, nonpharmacological therapies, pharmacological treatments, and surgical procedures, with the latter 2 categories being the major cost drivers. Complementary and alternative medicine (CAM) therapies are a newly recognized component of the dry eye economic burden. There is wide variation in patterns of diagnosis and treatment, but current therapies are not universally effective. Given the prevalence of the condition, indirect costs may be large. Utilization of pharmacological therapies, especially those other than tear replacements, the extent of CAM use, cost of complications of surgical procedures, and indirect costs are unknown. The natural history and probability that patients will transition between therapies, based on underlying disease severity, need to be elucidated. Conclusions: Dry eye is a prevalent condition with the potential for a high economic burden; additional studies are needed to further characterize the economic impact.

CONTROLLED TERM: Medical Descriptors:

- \*dry eye: DI, diagnosis
- \*dry eye: DM, disease management
- \*dry eye: DT, drug therapy
- \*dry eye: ET, etiology
- \*dry eye: SI, side effect
- \*dry eye: SU, surgery
- \*dry eye: TH, therapy
- \*economic aspect
- disease severity
- resource management
- health care personnel
- economic evaluation
- health care cost
- clinical feature
- practice guideline
- treatment indication
  - cataract: SI, side effect
  - glaucoma: SI, side effect
- superinfection: SI, side effect
- drug indication
- alternative medicine
- acupuncture
- diet supplementation

blepharitis: DT, drug therapy  
eye surgery  
cost benefit analysis  
drug cost  
medical fee  
keratomileusis  
human  
article  
priority journal  
Drug Descriptors:  
amiodarone: AE, adverse drug reaction  
antidepressant agent: AE, adverse drug reaction  
neuroleptic agent: AE, adverse drug reaction  
isotretinoin: AE, adverse drug reaction  
interferon: AE, adverse drug reaction  
artificial tear  
corticosteroid: AE, adverse drug reaction  
corticosteroid: DT, drug therapy  
corticosteroid: PE, pharmacoeconomics  
corticosteroid: TP, topical drug administration  
  cyclosporin: DT, drug therapy  
  cyclosporin: PE, pharmacoeconomics  
  cyclosporin: TP, topical drug administration  
  linseed oil: DT, drug therapy  
  linseed oil: PE, pharmacoeconomics  
fish oil: DT, drug therapy  
fish oil: PE, pharmacoeconomics  
antibiotic agent: DT, drug therapy  
antibiotic agent: PE, pharmacoeconomics  
antibiotic agent: PO, oral drug administration  
antibiotic agent: TP, topical drug administration  
pilocarpine: DT, drug therapy  
pilocarpine: PO, oral drug administration  
cevimeline: DT, drug therapy  
nonsteroid antiinflammatory agent: DT, drug therapy  
nonsteroid antiinflammatory agent: PE, pharmacoeconomics  
tsukubaenolide: DT, drug therapy  
eledoisin: PD, pharmacology  
purinergic receptor stimulating agent: PD, pharmacology  
n,n dimethylphenethylamine  
androgen  
estrogen  
retinol  
botulinum toxin  
antioxidant: PO, oral drug administration  
zidovudine  
calcium  
antivirus agent  
antihistaminic agent: DT, drug therapy  
antihistaminic agent: PE, pharmacoeconomics  
unclassified drug

CAS REGISTRY NO.: (amiodarone) 1951-25-3, 19774-82-4, 62067-87-2;  
(isotretinoin) 4759-48-2; (cyclosporin)  
79217-60-0; (linseed oil) 8001-26-1; (fish oil) 8016-13-5;  
(pilocarpine) 148-72-1, 54-71-7, 92-13-7; (cevimeline)  
107220-27-9, 107220-28-0, 107233-08-9, 153504-70-2;  
(tsukubaenolide) 104987-11-3; (eledoisin) 69-25-0;  
(retinol) 68-26-8, 82445-97-4; (zidovudine) 30516-87-1;  
(calcium) 7440-70-2

CHEMICAL NAME: Af 2975

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ACCESSION NUMBER: 2004180365 EMBASE Full-text  
TITLE: Lacrimostimulants and lacrimomimetics.  
AUTHOR: Grahn B.H.; Storey E.S.  
CORPORATE SOURCE: B.H. Grahn, Dept. of Small Animal Clinical Sci., Western College of Veterinary Med., University of Saskatchewan, 52 Campus Drive, Saskatoon, Sask. S7N 5B4, Canada. bruce.grahn@usask.ca  
SOURCE: Veterinary Clinics of North America - Small Animal Practice, (2004) Vol. 34, No. 3, pp. 739-753. .  
Refs: 64  
ISSN: 0195-5616 CODEN: VCNA66  
PUBLISHER IDENT.: S 0195-5616(03)00187-6  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
012 Ophthalmology  
030 Pharmacology  
037 Drug Literature Index  
052 Toxicology  
LANGUAGE: English  
ENTRY DATE: Entered STN: 13 May 2004  
Last Updated on STN: 13 May 2004  
CONTROLLED TERM: Medical Descriptors:  
\*tear film  
\*lacrimal gland disease: DT, drug therapy  
\*lacrimal gland disease: ET, etiology  
clinical feature  
diagnostic procedure  
treatment outcome  
lacrimal gland  
goblet cell  
nictitating membrane  
meibomian gland  
ophthalmology  
veterinary medicine  
drug tissue level  
drug blood level  
drug structure  
lacrimation  
dry eye: DT, drug therapy  
nonhuman  
review  
CONTROLLED TERM: Drug Descriptors:  
\*immunomodulating agent: AN, drug analysis  
\*immunomodulating agent: CM, drug comparison  
\*immunomodulating agent: CR, drug concentration  
\*immunomodulating agent: DT, drug therapy  
\*immunomodulating agent: TO, drug toxicity  
\*immunomodulating agent: PD, pharmacology  
\*immunomodulating agent: TP, topical drug administration  
\*cholinergic receptor stimulating agent: CB, drug combination  
\*cholinergic receptor stimulating agent: DT, drug therapy  
\*cholinergic receptor stimulating agent: TO, drug toxicity  
\*cholinergic receptor stimulating agent: PD, pharmacology  
\*cholinergic receptor stimulating agent: PO, oral drug administration

\*cholinergic receptor stimulating agent: TP, topical drug administration  
\*electrolyte: DT, drug therapy  
\*electrolyte: PD, pharmacology  
  cyclosporin: AN, drug analysis  
  cyclosporin: CM, drug comparison  
  cyclosporin: CR, drug concentration  
  cyclosporin: DT, drug therapy  
  cyclosporin: TO, drug toxicity  
  cyclosporin: PD, pharmacology  
  cyclosporin: TP, topical drug administration  
tsukubaenolide: AN, drug analysis  
tsukubaenolide: CM, drug comparison  
tsukubaenolide: DT, drug therapy  
tsukubaenolide: TO, drug toxicity  
tsukubaenolide: PD, pharmacology  
tsukubaenolide: TP, topical drug administration  
rapamycin: CM, drug comparison  
rapamycin: DT, drug therapy  
rapamycin: PD, pharmacology  
rapamycin: TP, topical drug administration  
pilocarpine: CB, drug combination  
pilocarpine: DT, drug therapy  
pilocarpine: TO, drug toxicity  
pilocarpine: PD, pharmacology  
pilocarpine: PO, oral drug administration  
pilocarpine: TP, topical drug administration  
calcineurin inhibitor: AN, drug analysis  
calcineurin inhibitor: CM, drug comparison  
calcineurin inhibitor: DT, drug therapy  
calcineurin inhibitor: TO, drug toxicity  
calcineurin inhibitor: PD, pharmacology  
calcineurin inhibitor: TP, topical drug administration  
nonsteroid antiinflammatory agent: CB, drug combination  
nonsteroid antiinflammatory agent: DT, drug therapy  
anesthetic agent: CB, drug combination  
anesthetic agent: DT, drug therapy  
polyvinyl alcohol: CB, drug combination  
polyvinyl alcohol: DT, drug therapy  
carboxymethylcellulose: DT, drug therapy  
hydroxypropylmethylcellulose: CB, drug combination  
hydroxypropylmethylcellulose: DT, drug therapy  
hydroxymethylcellulose: DT, drug therapy  
methylcellulose: DT, drug therapy  
polymer: CB, drug combination  
polymer: DT, drug therapy  
dextran 70: CB, drug combination  
dextran 70: DT, drug therapy  
povidone: CB, drug combination  
povidone: DT, drug therapy  
dextran: CB, drug combination  
dextran: DT, drug therapy  
glycerol: CB, drug combination  
glycerol: DT, drug therapy  
polycarbophil: CB, drug combination  
polycarbophil: DT, drug therapy  
  macrogol: CB, drug combination  
  macrogol: DT, drug therapy  
petroleum: CB, drug combination  
petroleum: DT, drug therapy

mineral oil: CB, drug combination  
mineral oil: DT, drug therapy  
lanolin: CB, drug combination  
lanolin: DT, drug therapy  
hyaluronic acid derivative: DT, drug therapy  
benzalkonium chloride  
thiomersal  
chlorbutol  
unindexed drug  
akwa tears  
liquifilm forte  
liquifilm tears  
dry eyes  
hypotears  
hypotears pf  
ocutears  
ocutears pf  
tearfair solution  
theratears  
celluvisc lubricant  
refresh tears  
lacri lubricant  
refresh plus  
isopto alkaline  
comfort tears  
murocell  
genteal lubricating eye drops  
tearisol  
teargard  
lubrifair  
naphazoline  
tears renewed  
adsorbotear  
bio tears  
tear naturale ii  
tear naturale  
free tears plus  
lubri tears  
moisture drops  
aquasite  
lubrifair solution  
murine eye lubricant  
natures tears  
duratears naturale  
lacrilube  
lacrilube np  
lacrilube sop  
refresh pm  
duolobe  
lipotears  
ocutube  
petroleum ointment  
hyashield  
hyashield nite  
dry eye therapy  
eye lube a

CAS REGISTRY NO.: (cyclosporin) 79217-60-0; (tsukubaenolide)  
104987-11-3; (rapamycin) 53123-88-9; (pilocarpine)  
148-72-1, 54-71-7, 92-13-7; (polyvinyl alcohol) 37380-95-3,  
9002-89-5; (carboxymethylcellulose) 8050-38-2, 9000-11-7,

9004-32-4, 9050-04-8; (hydroxypropylmethylcellulose)  
9004-65-3; (hydroxymethylcellulose) 37353-59-6;  
(methylcellulose) 79484-92-7, 9004-67-5; (povidone)  
9003-39-8; (dextran) 87915-38-6, 9014-78-2; (glycerol)  
56-81-5; (polycarbophil) 9003-97-8; (macrogol) 25322-68-3;  
(petroleum) 8002-05-9; (lanolin) 70321-63-0, 8006-54-0,  
8020-84-6, 8031-44-5, 8038-28-6; (benzalkonium chloride)  
66331-30-4, 78244-97-0, 81181-32-0; (thiomersal) 54-64-8;  
(chlorbutol) 57-15-8; (naphazoline) 5144-52-5, 550-99-2,  
835-31-4

CHEMICAL NAME: (1) Akwa tears; (2) Liquifilm forte; (3) Liquifilm tears;  
(4) Dry eyes; (5) Hypotears; (6) Hypotears pf; (7)  
Ocutears; (8) Ocutears pf; (9) Tearfair solution; (10)  
Theratears; (11) Celluvisc lubricant; (12) Refresh tears;  
(13) Lacri lubricant; (14) Refresh plus; (15) Cellufresh;  
(16) Isopto alkaline; (17) Isopto tears; (18) Comfort  
tears; (19) Murocell; (20) Genteal lubricating eye drops;  
(21) Tearisol; (22) Teargard; (23) Lubrifair; (24) Clear  
eyes; (25) Tears renewed; (26) Adsorbotear; (27) Bio tears;  
(28) Tear naturale ii; (29) Tear naturale; (30) Free tears  
plus; (31) Lubri tears; (32) Moisture drops; (33) Aquasite;  
(34) Hypotears; (35) Hypotears pf; (36) Lubrifair solution;  
(37) Murine eye lubricant; (38) Natures tears; (39)  
Duratears naturale; (40) Lacrilube; (41) Lacrilube np; (42)  
Lacrilube sop; (43) Refresh pm; (44) Duolobe; (45)  
Lipotears; (46) Ocutube; (47) Petroleum ointment; (48)  
Hyashield; (49) Hyashield nite; (50) Dry eye therapy; (51)  
Eye lube a; Fk 506

COMPANY NAME: (10) Advanced Vision Research; (18) Barnes Hind; (22) Med  
tec; (25) Akorn; (33) Ciba Vision; (35) Iolab; (37) Ross;  
(38) Rugby; (39) Alcon; (43) Allergan; (45) Coopervision;  
(46) Ocumed; (47) Pharmafair; (49) I-Med; (50) Bausch and  
Lomb; (51) Optoptics

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ACCESSION NUMBER: 2004505791 EMBASE Full-text

TITLE: Immunomodulatory therapy in ophthalmology - Is there a  
place for topical application?.

AUTHOR: Bertelmann E.; Pleyer U.

CORPORATE SOURCE: E. Bertelmann, Augenklinik Charite, Universitätsmedizin  
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SOURCE: Ophthalmologica, (2004) Vol. 218, No. 6, pp. 359-367. .  
Refs: 71

ISSN: 0030-3755 CODEN: OPHTAD

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 012 Ophthalmology  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
038 Adverse Reactions Titles  
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 9 Dec 2004

Last Updated on STN: 9 Dec 2004

ABSTRACT: Topical corticosteroids, although effective in the treatment of ocular  
immune-mediated diseases, are well known for their ocular side-effects.

Not surprisingly, a variety of alternative immunomodulatory agents have been

tested for topical use including cyclosporin A (CsA), mycophenolate mofetil (MMF), tacrolimus (FK506), rapamycin (sirolimus) and leflunomide. Local application bears the possibility to avoid the severe side-effects of systemic therapy. The effect of topical therapy is naturally restricted to local immune response mechanisms, such as antigen presentation by Langerhans and dendritic cells. Moreover, many immunomodulatory agents (e.g. CsA) are lipophilic and thus have low water solubility and penetrate insufficiently intraocularly, often being stored in the lipophilic corneal epithelial barrier. Therefore, the therapeutical success is limited for intra-ocular immune-mediated diseases like anterior uveitis. However, a multitude of strategies have been introduced to circumvent these problems including complexing substances such as cyclodextrins (CDs) and liposomes. In the prevention and treatment of transplant rejection after keratoplasty, many attempts to introduce topical immunomodulatory therapy have failed; on the other hand, further therapeutic options not primarily expected are being evaluated today such as treatment of severe keratoconjunctivitis sicca. In our own studies, we investigated the pharmacokinetics of topical treatment with different agents including MMF and evaluated the efficacy of topical treatment in animal models for uveitis and keratoplasty. Taken together, topical immunomodulatory therapy will not replace systemic therapy but further treatment options can be expected. Copyright .COPYRGT. 2004 S. Karger AG, Basel.

CONTROLLED TERM: Medical Descriptors:  
 \*immunomodulation  
 drug mechanism  
 drug activity  
 drug synthesis  
 drug formulation  
 drug bioavailability  
 acquired immune deficiency syndrome: DT, drug therapy  
   cornea disease: DT, drug therapy  
   cornea disease: PC, prevention  
   dry eye: DT, drug therapy  
   eye disease: DT, drug therapy  
 nephrotoxicity: SI, side effect  
 graft rejection: CO, complication  
 graft rejection: DT, drug therapy  
 graft rejection: PC, prevention  
 penetrating keratoplasty  
 immunopathology: DT, drug therapy  
 treatment outcome  
 side effect: SI, side effect  
 topical treatment  
 immune response  
 antigen presentation  
 Langerhans cell  
 dendritic cell  
 lipophilicity  
 drug solubility  
 drug penetration  
   iridocyclitis: DT, drug therapy  
 treatment failure  
 disease severity  
   keratoconjunctivitis sicca: DT, drug therapy  
 drug tissue level  
 aqueous solution  
 gel  
 rheumatoid arthritis: DT, drug therapy  
 virus infection: DT, drug therapy  
   herpes simplex keratitis: DT, drug therapy

atopy: DT, drug therapy  
vernal conjunctivitis: DT, drug therapy  
cornea ulcer: DT, drug therapy  
Sjogren syndrome: DT, drug therapy  
graft versus host reaction: CO, complication  
graft versus host reaction: DT, drug therapy  
graft versus host reaction: PC, prevention  
postoperative complication: CO, complication  
postoperative complication: DT, drug therapy  
human  
nonhuman  
clinical trial  
review

CONTROLLED TERM:

Drug Descriptors:  
\*immunomodulating agent: AE, adverse drug reaction  
\*immunomodulating agent: AD, drug administration  
\*immunomodulating agent: AN, drug analysis  
\*immunomodulating agent: CB, drug combination  
\*immunomodulating agent: CM, drug comparison  
\*immunomodulating agent: CR, drug concentration  
\*immunomodulating agent: DO, drug dose  
\*immunomodulating agent: DT, drug therapy  
\*immunomodulating agent: IP, intraperitoneal drug administration  
\*immunomodulating agent: PO, oral drug administration  
\*immunomodulating agent: PA, parenteral drug administration  
\*immunomodulating agent: PR, pharmaceuticals  
\*immunomodulating agent: PK, pharmacokinetics  
\*immunomodulating agent: PD, pharmacology  
\*immunomodulating agent: TP, topical drug administration  
\*cyclosporin A: AN, drug analysis  
\*cyclosporin A: CB, drug combination  
\*cyclosporin A: CM, drug comparison  
\*cyclosporin A: CR, drug concentration  
\*cyclosporin A: DO, drug dose  
\*cyclosporin A: DT, drug therapy  
\*cyclosporin A: PR, pharmaceuticals  
\*cyclosporin A: PK, pharmacokinetics  
\*cyclosporin A: PD, pharmacology  
\*cyclosporin A: TP, topical drug administration  
\*mycophenolic acid 2 morpholinoethyl ester: CT, clinical trial  
\*mycophenolic acid 2 morpholinoethyl ester: CB, drug combination  
\*mycophenolic acid 2 morpholinoethyl ester: CM, drug comparison  
\*mycophenolic acid 2 morpholinoethyl ester: CR, drug concentration  
\*mycophenolic acid 2 morpholinoethyl ester: DT, drug therapy  
\*mycophenolic acid 2 morpholinoethyl ester: PR, pharmaceuticals  
\*mycophenolic acid 2 morpholinoethyl ester: PK, pharmacokinetics  
\*mycophenolic acid 2 morpholinoethyl ester: PD, pharmacology  
\*tsukubaenolide: AE, adverse drug reaction  
\*tsukubaenolide: CM, drug comparison  
\*tsukubaenolide: DT, drug therapy  
\*tsukubaenolide: PR, pharmaceuticals



\*tsukubaenolide: PD, pharmacology  
 \*tsukubaenolide: TP, topical drug administration  
 \*rapamycin: AE, adverse drug reaction  
 \*rapamycin: AN, drug analysis  
 \*rapamycin: CM, drug comparison  
 \*rapamycin: IP, intraperitoneal drug administration  
 \*rapamycin: PA, parenteral drug administration  
 \*rapamycin: PD, pharmacology  
 prednisolone acetate: PD, pharmacology  
 macrolide: AN, drug analysis  
 macrolide: CB, drug combination  
 macrolide: CM, drug comparison  
 macrolide: CR, drug concentration  
 macrolide: DO, drug dose  
 macrolide: DT, drug therapy  
 macrolide: PR, pharmaceuticals  
 macrolide: PK, pharmacokinetics  
 macrolide: PD, pharmacology  
 macrolide: TP, topical drug administration  
 amphotericin B: PR, pharmaceuticals  
 chloramphenicol: PR, pharmaceuticals  
 carbonate dehydratase inhibitor: PR, pharmaceuticals  
 nonsteroid antiinflammatory agent: PR, pharmaceuticals  
 diclofenac: PR, pharmaceuticals  
 thalidomide: PR, pharmaceuticals  
 liposome: PR, pharmaceuticals  
 everolimus: PO, oral drug administration  
 everolimus: PD, pharmacology  
 steroid: CB, drug combination  
 steroid: CM, drug comparison  
 azathioprine: CB, drug combination  
 azathioprine: CM, drug comparison  
 corticosteroid: AE, adverse drug reaction  
 corticosteroid: DT, drug therapy  
 corticosteroid: TP, topical drug administration  
 cyclodextrin: PR, pharmaceuticals  
 oligosaccharide: PR, pharmaceuticals  
 eye drops: PR, pharmaceuticals  
 eye drops: TP, topical drug administration  
 eye ointment: PR, pharmaceuticals  
 eye ointment: TP, topical drug administration  
 chitosan: PR, pharmaceuticals  
 chitosan: TP, topical drug administration  
     water oil cream: PR, pharmaceuticals  
     water oil cream: TP, topical drug administration

CAS REGISTRY NO.: (cyclosporin A) 59865-13-3, 63798-73-2; (mycophenolic acid  
 2 morpholinoethyl ester) 116680-01-4, 128794-94-5;  
 (tsukubaenolide) 104987-11-3; (rapamycin) 53123-88-9;  
 (prednisolone acetate) 52-21-1, 52628-64-5; (amphotericin  
 B) 1397-89-3, 30652-87-0; (chloramphenicol) 134-90-7,  
 2787-09-9, 56-75-7; (diclofenac) 15307-79-6, 15307-86-5;  
 (thalidomide) 50-35-1; (everolimus) 159351-69-6;  
 (azathioprine) 446-86-6; (cyclodextrin) 12619-70-4;  
 (chitosan) 9012-76-4

CHEMICAL NAME: Fk 506

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ACCESSION NUMBER: 2004199621 EMBASE Full-text  
 TITLE: Vernal keratoconjunctivitis.

AUTHOR: Bonini S.; Coassin M.; Aronni S.; Lambiase A.  
CORPORATE SOURCE: S. Bonini, Interdisciplinary Ctr. Biomed. Res., Laboratory  
of Ophthalmology, University of Rome, Via Emilio Longoni  
83, 00155 Rome, Italy. sbonini@mcclink.it  
SOURCE: Eye, (2004) Vol. 18, No. 4, pp. 345-351. .  
Refs: 69  
ISSN: 0950-222X CODEN: EYEEEC  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
012 Ophthalmology  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
038 Adverse Reactions Titles  
039 Pharmacy  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20 May 2004  
Last Updated on STN: 20 May 2004

ABSTRACT: Vernal keratoconjunctivitis (VKC) is an allergic eye disease that especially affects young boys. The most common symptoms are itching, photophobia, burning, and tearing. The most common signs are giant papillae, superficial keratitis, and conjunctival hyperaemia. Patients with VKC frequently have a family or medical history of atopic diseases, such as asthma, rhinitis, and eczema. However, VKC is not associated with a positive skin test or RAST in 42-47% of patients, confirming that it is not solely an IgE-mediated disease. On the basis of challenge studies as well as immunohistochemical and mediator studies, a Th2-driven mechanism with the involvement of mast cells, eosinophils, and lymphocytes has been suggested. Th2 lymphocytes are responsible for both hyperproduction of IgE (interleukin 4, IL-4) and for differentiation and activation of mast cells (IL-3) and eosinophils (IL-5). Other studies have demonstrated the involvement of neural factors such as substance P and NGF in the pathogenesis of VKC, and the overexpression of oestrogen and progesterone receptors in the conjunctiva of VKC patients has introduced the possible involvement of sex hormones. Thus, the pathogenesis of VKC is probably multifactorial, with the interaction of the immune, nervous, and endocrine systems. The clinical management of VKC requires a swift diagnosis, correct therapy, and evaluation of the prognosis. The diagnosis is generally based on the signs and symptoms of the disease, but in difficult cases can be aided by conjunctival scraping, demonstrating the presence of infiltrating eosinophils. Therapeutic options are many, in most cases topical, and should be chosen on the basis of the severity of the disease. The most effective drugs, steroids, should however be carefully administered, and only for brief periods, to avoid secondary development of glaucoma. A 2% solution of **cyclosporine** in olive oil or in castor oil should be considered as an alternative. The long-term prognosis of patients is generally good; however 6% of patients develop corneal damage, cataract, or glaucoma. .COPYRGT. 2004 Nature Publishing Group All rights reserved.

CONTROLLED TERM: Medical Descriptors:  
\*vernal conjunctivitis: DI, diagnosis  
\*vernal conjunctivitis: DT, drug therapy  
\*vernal conjunctivitis: ET, etiology  
allergic disease: DI, diagnosis  
allergic disease: DT, drug therapy  
allergic disease: ET, etiology  
symptomatology  
pruritus  
photophobia  
burning sensation

lacrimation  
    **keratitis**  
        **conjunctival hyperemia**  
family history  
anamnesis  
disease association  
skin test  
immunopathogenesis  
immunohistochemistry  
Th2 cell  
mast cell  
eosinophil  
lymphocyte activation  
immunoglobulin production  
cell differentiation  
gene overexpression  
diagnostic value  
prognosis  
cell infiltration  
treatment planning  
disease severity  
    **glaucoma: SI, side effect**  
drug efficacy  
drug formulation  
    **cornea injury: CO, complication**  
    **cataract: CO, complication**  
outcomes research  
human  
review  
Drug Descriptors:  
immunoglobulin E: EC, endogenous compound  
interleukin 4: EC, endogenous compound  
interleukin 3: EC, endogenous compound  
interleukin 5: EC, endogenous compound  
substance P: EC, endogenous compound  
nerve growth factor: EC, endogenous compound  
estrogen receptor: EC, endogenous compound  
progesterone receptor: EC, endogenous compound  
sex hormone: EC, endogenous compound  
steroid: AE, adverse drug reaction  
steroid: DT, drug therapy  
steroid: PD, pharmacology  
steroid: TP, topical drug administration  
    **cyclosporin A: CB, drug combination**  
    **cyclosporin A: DT, drug therapy**  
    **cyclosporin A: PR, pharmaceuticals**  
    **olive oil: CB, drug combination**  
    **olive oil: DT, drug therapy**  
    **olive oil: PR, pharmaceuticals**  
castor oil: CB, drug combination  
castor oil: DT, drug therapy  
castor oil: PR, pharmaceuticals  
cromoglycate disodium: DT, drug therapy  
cromoglycate disodium: PD, pharmacology  
cromoglycate disodium: TP, topical drug administration  
lodoxamide trometamol: DT, drug therapy  
lodoxamide trometamol: PD, pharmacology  
lodoxamide trometamol: TP, topical drug administration  
nedocromil sodium: DT, drug therapy  
nedocromil sodium: PD, pharmacology

nedocromil sodium: TP, topical drug administration  
spaglumic acid: DT, drug therapy  
spaglumic acid: PD, pharmacology  
spaglumic acid: TP, topical drug administration  
antiallergic agent: DT, drug therapy  
antiallergic agent: PD, pharmacology  
antiallergic agent: TP, topical drug administration  
antihistaminic agent: CM, drug comparison  
antihistaminic agent: DT, drug therapy  
antihistaminic agent: PD, pharmacology  
antihistaminic agent: PO, oral drug administration  
antihistaminic agent: TP, topical drug administration  
nonsteroid antiinflammatory agent: DT, drug therapy  
nonsteroid antiinflammatory agent: PD, pharmacology  
nonsteroid antiinflammatory agent: TP, topical drug administration  
acetylsalicylic acid: CM, drug comparison  
acetylsalicylic acid: DT, drug therapy  
acetylsalicylic acid: PD, pharmacology  
montelukast: CM, drug comparison  
montelukast: DT, drug therapy  
montelukast: PD, pharmacology  
montelukast: PO, oral drug administration  
unclassified drug

CAS REGISTRY NO.: (immunoglobulin E) 37341-29-0; (substance P) 33507-63-0;  
(nerve growth factor) 9061-61-4; (cyclosporin  
A) 59865-13-3, 63798-73-2; (olive oil)  
8001-25-0; (castor oil) 8001-79-4; (cromoglycate disodium)  
15826-37-6, 16110-51-3, 93356-79-7, 93356-84-4; (lodoxamide  
trometamol) 63610-09-3; (nedocromil sodium) 69049-74-7;  
(acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4,  
53664-49-6, 63781-77-1; (montelukast) 151767-02-1,  
158966-92-8

CHEMICAL NAME: Aspirin

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ACCESSION NUMBER: 2004309369 EMBASE [Full-text](#)  
TITLE: Sjogren's syndrome.  
AUTHOR: Venables P.J.W.  
CORPORATE SOURCE: Dr. P.J.W. Venables, Kennedy Inst. of Rheumatology Div.,  
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SOURCE: Best Practice and Research in Clinical Rheumatology, (2004)  
Vol. 18, No. 3, pp. 313-329. .  
Refs: 48  
ISSN: 1521-6942 CODEN: BPRCC7  
PUBLISHER IDENT.: S 1521-6942(04)00036-1  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
030 Pharmacology  
031 Arthritis and Rheumatism  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 5 Aug 2004  
Last Updated on STN: 5 Aug 2004

ABSTRACT: Sjogren's syndrome is an autoimmune disease characterized by inflammation of the exocrine glands, leading to impaired function. Here, I review the relatively short history of the syndrome and explain why it is frequently underdiagnosed, undertreated and under-researched. Attempts to provide classification criteria have culminated in the revised American-European Consensus Criteria, which provide a sound basis for both clinical management and research. The recognition that Sjogren's syndrome is a disease of considerable morbidity has led to a more aggressive approach to therapy ranging from topical therapies to systemic treatment with secretagogues such as pilocarpine and cevimeline, and immunomodulatory drugs such as hydroxychloroquine and interferon-alpha. The central role of the glandular epithelial cell is identified as the key to understanding the pathogenesis of the disease. Hypofunction rather than destruction of these cells is now regarded as the main mechanism of secretory failure in Sjogren's syndrome.  
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CONTROLLED TERM: Medical Descriptors:  
\*Sjogren syndrome: DI, diagnosis  
\*Sjogren syndrome: DT, drug therapy  
\*Sjogren syndrome: ET, etiology  
autoimmune disease: DI, diagnosis  
autoimmune disease: DT, drug therapy  
autoimmune disease: ET, etiology  
exocrine gland  
inflammation  
diagnostic error  
medical research  
disease classification  
consensus development  
morbidity  
epithelium cell  
exocrine cell  
cell function  
pathogenesis  
cell destruction  
dry eye: CO, complication  
dry eye: DT, drug therapy  
flushing  
skin manifestation: SI, side effect  
sweat gland disease: SI, side effect  
diarrhea: SI, side effect  
urinary frequency  
micturition disorder: SI, side effect  
headache: SI, side effect  
abdominal pain: SI, side effect  
nausea: SI, side effect  
drug selectivity  
human  
clinical trial  
review  
priority journal  
Drug Descriptors:  
pilocarpine: AE, adverse drug reaction  
pilocarpine: DT, drug therapy  
pilocarpine: TP, topical drug administration  
cevimeline: AE, adverse drug reaction  
cevimeline: CT, clinical trial  
cevimeline: DT, drug therapy  
cevimeline: PD, pharmacology  
cevimeline: TP, topical drug administration

immunomodulating agent: DT, drug therapy  
hydroxychloroquine sulfate: DT, drug therapy  
alpha interferon: DT, drug therapy  
steroid: CT, clinical trial  
steroid: DT, drug therapy  
cyclophosphamide: DT, drug therapy  
tears naturale: DT, drug therapy  
tears naturale: TP, topical drug administration  
polyvinyl alcohol: DT, drug therapy  
polyvinyl alcohol: TP, topical drug administration  
hydroxypropylmethylcellulose: DT, drug therapy  
hydroxypropylmethylcellulose: TP, topical drug administration  
carbomer: DT, drug therapy  
carbomer: TP, topical drug administration  
    **paraffin: DT, drug therapy**  
    **paraffin: TP, topical drug administration**  
acetylcysteine: DT, drug therapy  
acetylcysteine: TP, topical drug administration  
methotrexate: CT, clinical trial  
methotrexate: DT, drug therapy  
    **cyclosporin: CT, clinical trial**  
    **cyclosporin: DT, drug therapy**  
azathioprine: CT, clinical trial  
azathioprine: DT, drug therapy  
cytotoxic agent: DT, drug therapy  
infliximab: DT, drug therapy  
B lymphocyte antibody: DT, drug therapy  
rituximab: DT, drug therapy  
liquifilm  
viscotears  
geltears  
lacri lube  
lubri tears  
ilube  
glandosane  
luborant  
saliva substitute  
oralbalance  
bioextra

CAS REGISTRY NO.: (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (cevimeline)  
107220-27-9, 107220-28-0, 107233-08-9, 153504-70-2;  
(hydroxychloroquine sulfate) 747-36-4; (cyclophosphamide)  
50-18-0; (polyvinyl alcohol) 37380-95-3, 9002-89-5;  
(hydroxypropylmethylcellulose) 9004-65-3; (carbomer)  
9007-20-9, 9062-04-8; (acetylcysteine) 616-91-1;  
(methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (  
**cyclosporin**) 79217-60-0; (azathioprine) 446-86-6; .  
(infliximab) 170277-31-3; (rituximab) 174722-31-7; (lacri  
lube) 78200-24-5

CHEMICAL NAME: Salagen; Bioextra; Oralbalance; Saliva orthana; Luborant;  
Glandosane; Ilube; Lubri tears; Lacri lube; Geltears;  
Viscotears; Liquifilm; Sno tears; Tears naturale

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ACCESSION NUMBER: 2004377151 EMBASE Full-text  
TITLE: [Biological availability of ophthalmic preparations 2. Ophthalmic therapeutic systems].  
BIOLOGICKA DOSTUPNOST OCNICH LEKU 2. OCNI TERAPEUTICKE

SYSTEMY.  
AUTHOR: Masteikova R.; Chalupova Z.; Savickas A.  
CORPORATE SOURCE: R. Masteikova, Palackeho 1/3, 612 42 Brno, Czech Republic.  
masteikovar@vfu.cz  
SOURCE: Ceska a Slovenska Farmacie, (2004) Vol. 53, No. 5, pp.  
211-218. .  
Refs: 122  
ISSN: 1210-7816 CODEN: CSLFEK  
COUNTRY: Czech Republic  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 004 Microbiology  
012 Ophthalmology  
037 Drug Literature Index  
039 Pharmacy  
LANGUAGE: Czech  
SUMMARY LANGUAGE: English; Czech  
ENTRY DATE: Entered STN: 24 Sep 2004  
Last Updated on STN: 24 Sep 2004

ABSTRACT: Ophthalmic therapeutic systems, which rank among the drugs of the second and third generation, make possible prolonged and controlled drug release, or the introduction of the drug direct into the site of action (a specific eye tissue) with minimal distribution into the adjacent tissues. The group mainly consists of solid ophthalmic preparations, in a lesser extent there are systems developed from hydrogels, colloidal carriers, etc. The present review lists both insoluble ophthalmic therapeutic systems and those soluble in water (degradable, erodible). Insoluble systems include membrane-controlled ophthalmic therapeutic systems (e.g. Ocusert®), therapeutic eye lenses, eye implants, and other insoluble preparations. In the group of soluble preparations, topical inserts and systems are described, which are introduced into eye tissues as implants or injections.

CONTROLLED TERM: Medical Descriptors:  
\*eye disease: DT, drug therapy  
\*drug implant  
\*eye implant  
\*eye insert  
\*therapeutic eye lens  
\*ophthalmic therapeutic system  
\*soluble ocular drug insert  
acquired immune deficiency syndrome  
cytomegalovirus infection: CO, complication  
cytomegalovirus infection: DT, drug therapy  
retinitis: CO, complication  
retinitis: DT, drug therapy  
bioavailability  
solubility  
drug release.  
controlled drug release  
drug delivery system  
hydrogel  
colloid  
human  
review  
Drug Descriptors:  
\*pilocarpine: PR, pharmaceuticals  
\*agents acting on the eye: DT, drug therapy  
\*agents acting on the eye: PR, pharmaceuticals  
\*agents acting on the eye: TP, topical drug administration  
antivirus agent: DT, drug therapy  
antivirus agent: PR, pharmaceuticals

ganciclovir: DT, drug therapy  
 ganciclovir: PR, pharmaceuticals  
 corticosteroid: DT, drug therapy  
 corticosteroid: PR, pharmaceuticals  
 fluocinolone: DT, drug therapy  
 fluocinolone: PR, pharmaceuticals  
 triamcinolone: DT, drug therapy  
 triamcinolone: PR, pharmaceuticals  
     **cyclosporin: DT, drug therapy**  
     **cyclosporin: PR, pharmaceuticals**  
 amphotericin B: DT, drug therapy  
 amphotericin B: PR, pharmaceuticals  
 antibiotic agent: DT, drug therapy  
 antibiotic agent: PR, pharmaceuticals  
 ciprofloxacin: DT, drug therapy  
 ciprofloxacin: PR, pharmaceuticals  
 fluorouracil: DT, drug therapy  
 fluorouracil: PR, pharmaceuticals  
 polymer  
     **macrogol**  
 polymacon  
 povidone  
 polyacrylic acid  
 collagen  
 hyaluronic acid  
 xanthan  
 fibrin  
 methylcellulose  
 hydroxypropylmethylcellulose  
 hydroxypropylcellulose  
 ethyl cellulose  
 chitosan  
 polyvinyl acetate  
 eudragit  
 eudragit rs  
 unindexed drug

CAS REGISTRY NO.: (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (ganciclovir) 82410-32-0; (fluocinolone) 807-38-5; (triamcinolone) 124-94-7; (**cyclosporin**) 79217-60-0; (amphotericin B) 1397-89-3, 30652-87-0; (ciprofloxacin) 85721-33-1; (fluorouracil) 51-21-8; (macrogol) 25322-68-3; (polymacon) 25053-81-0, 25249-16-5, 98932-78-6; (povidone) 9003-39-8; (polyacrylic acid) 74350-43-9, 87003-46-1, 9003-01-4, 9003-04-7; (collagen) 9007-34-5; (hyaluronic acid) 31799-91-4, 9004-61-9, 9067-32-7; (xanthan) 11138-66-2; (fibrin) 9001-31-4; (methylcellulose) 79484-92-7, 9004-67-5; (hydroxypropylmethylcellulose) 9004-65-3; (hydroxypropylcellulose) 9004-64-2; (ethyl cellulose) 9004-57-3; (chitosan) 9012-76-4; (polyvinyl acetate) 9003-20-7; (eudragit) 24938-16-7, 51822-44-7, 9065-11-6; (eudragit rs) 33434-24-1

CHEMICAL NAME: (1) Ocuser; (2) Vitrasert; (3) Lacrisert  
 NAME OF PRODUCT: (1) Oculex Drug Delivery System; ProShield; New Ophthalmic Delivery System; Bio-Cor; Bioadhesive Ophthalmic Drug Insert; MediLens; Soluble Ocular Drug Insert  
 COMPANY NAME: (1) Alza; (2) Chiron; (3) Merck Sharp and Dohme  
 COMPANY NAME: (1) Oculex



ACCESSION NUMBER: 2004167588 EMBASE Full-text  
TITLE: Nanomedicines for overcoming biological barriers.  
AUTHOR: Alonso M.J.  
CORPORATE SOURCE: M.J. Alonso, Dept. Pharm. Pharmaceutical Technol., School  
of Pharmacy, Univ. Santiago de Compostela, Santiago de  
Compostela 15782, Spain. ffmjalon@usc.es  
SOURCE: Biomedicine and Pharmacotherapy, (2004) Vol. 58, No. 3, pp.  
168-172. .  
Refs: 26  
ISSN: 0753-3322 CODEN: BIPHEX  
PUBLISHER IDENT.: S 0753-3322(04)00013-7  
COUNTRY: France  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index  
039 Pharmacy  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 29 Apr 2004  
Last Updated on STN: 29 Apr 2004

ABSTRACT: Drug delivery is an interdisciplinary area of research that aims at making the administration of complex new drugs feasible, as well as adding critical value to the drugs that are currently in the market. At present, one of the most attractive areas of research in drug delivery is the design of nanomedicines consisting of nanosystems that are able to deliver drugs to the right place, at appropriate times. The goal of the present article is to review the advances we have made in the development and characterization of nanosystems intended to be used as drug carriers for mucosal administration. These nanocarriers are able to protect the associated drug against degradation and facilitate its transport across critical and specific barriers. Some of them, are further able to release the associated drug to the target tissue in a controlled manner. These nanocarriers have been made of safe materials, including synthetic biodegradable polymers, lipids and polysaccharides. A number of nanotechnologies have been developed that enable the association of a variety of drugs to these nanocarriers, ranging from classical small drug to large DNA fragments. The in vitro cell culture studies and the in vivo experiments have evidenced the potential of these nanocarriers for overcoming important mucosal barriers, such as the intestinal, nasal and ocular barriers. Hopefully, this will soon represent a strategy for making cheaper and faster, more efficacious medicines. .COPYRGT. 2004 Published by Elsevier SAS.

CONTROLLED TERM: Medical Descriptors:  
\*nanotechnology  
drug delivery system  
drug degradation  
drug transport  
biodegradability  
in vitro study  
cell culture  
nanoparticle  
drug absorption  
humoral immunity  
mucosal immunity  
cornea injury  
drug penetration  
nonhuman  
review  
priority journal  
Drug Descriptors:

\*drug carrier: AD, drug administration  
 \*drug carrier: NA, intranasal drug administration  
 \*drug carrier: PO, oral drug administration  
 \*drug carrier: PR, pharmaceuticals  
 \*drug carrier: TP, topical drug administration  
 polymer: PO, oral drug administration  
 polymer: PR, pharmaceuticals  
 lipid: NA, intranasal drug administration  
 lipid: PO, oral drug administration  
 lipid: PR, pharmaceuticals  
 polysaccharide: PR, pharmaceuticals  
 DNA fragment: PR, pharmaceuticals  
 chitosan: NA, intranasal drug administration  
 chitosan: PO, oral drug administration  
 chitosan: PR, pharmaceuticals  
 chitosan: TP, topical drug administration  
     macrogol: NA, intranasal drug administration  
     macrogol: PO, oral drug administration  
     macrogol: PR, pharmaceuticals  
     oil: NA, intranasal drug administration  
     oil: PO, oral drug administration  
     oil: PR, pharmaceuticals  
 polyester: NA, intranasal drug administration  
 polyester: PO, oral drug administration  
 polyester: PR, pharmaceuticals  
 polyester: TP, topical drug administration  
 polystyrene: PR, pharmaceuticals  
 insulin: NA, intranasal drug administration  
 insulin: PO, oral drug administration  
 insulin: PR, pharmaceuticals  
 insulin: PK, pharmacokinetics  
 poly(cyanoacrylate): TO, drug toxicity  
 poly(cyanoacrylate): PO, oral drug administration  
 poly(cyanoacrylate): PR, pharmaceuticals  
 poly(cyanoacrylate): TP, topical drug administration  
 nanocapsule: PO, oral drug administration  
 nanocapsule: PR, pharmaceuticals  
 copolymer: PO, oral drug administration  
 copolymer: PR, pharmaceuticals  
 DNA vaccine: NA, intranasal drug administration  
 DNA vaccine: PR, pharmaceuticals  
 tetanus toxin: NA, intranasal drug administration  
 tetanus toxin: PR, pharmaceuticals  
 tetanus toxin: PD, pharmacology  
 indometacin: PR, pharmaceuticals  
 indometacin: PK, pharmacokinetics  
 indometacin: TP, topical drug administration  
 cyclosporin A: IO, intraocular drug administration  
 cyclosporin A: PR, pharmaceuticals  
 cyclosporin A: PK, pharmacokinetics  
     cyclosporin A: TP, topical drug administration  
 unclassified drug  
 CAS REGISTRY NO.: (lipid) 66455-18-3; (chitosan) 9012-76-4; (macrogol)  
 25322-68-3; (polystyrene) 9003-53-6; (insulin) 9004-10-8;  
 (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (cyclosporin  
 A) 59865-13-3, 63798-73-2

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ACCESSION NUMBER: 2004194261 EMBASE Full-text

TITLE: Evaluation and Treatment of Dry Eye in Laser Vision Correction.  
AUTHOR: Pascucci S.E.  
CORPORATE SOURCE: Dr. S.E. Pascucci, Northeastern Eye Institute, 200 Mifflin Avenue, Scranton, PA 18503, United States. stevepascucci@ne-eye.com  
SOURCE: Clinical and Refractive Optometry, (2004) Vol. 15, No. 3, pp. 96-102. .  
Refs: 8  
ISSN: 1705-4850 CODEN: CROLA8  
COUNTRY: Canada  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 012 Ophthalmology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20 May 2004  
Last Updated on STN: 20 May 2004

ABSTRACT: Dry eye is a very widespread ocular condition and is one of the most common reasons patients seek help from eye care professionals. With the increasing acceptance and success of laser vision correction procedures, surgeons will likely be seeing more potential patients with dry eye. If careful patient evaluation for dry eye is performed and preoperative treatment is given, most patients with mild dry eye can successfully undergo laser vision correction surgery. However, some patients with dry eye may never be suitable candidates for this surgery.

CONTROLLED TERM: Medical Descriptors:  
\*dry eye: CO, complication  
\*dry eye: DT, drug therapy  
\*dry eye: ET, etiology  
\*dry eye: PC, prevention  
\*dry eye: TH, therapy  
\*visual impairment: SI, side effect  
\*visual impairment: SU, surgery  
\*keratomileusis  
\*laser epithelial keratomileusis  
surgeon  
surgical risk  
medical assessment  
preoperative care  
surgical patient  
antibiotic prophylaxis  
drug capsule  
drug formulation  
low drug dose  
eyelid closure  
human  
review  
Drug Descriptors:  
doxycycline: DT, drug therapy  
doxycycline: PO, oral drug administration  
tetracycline: DT, drug therapy  
tetracycline: PO, oral drug administration  
omega 3 fatty acid: DT, drug therapy  
essential fatty acid: DT, drug therapy  
essential fatty acid: PR, pharmaceuticals  
artificial tear: AE, adverse drug reaction  
artificial tear: TO, drug toxicity

fluorometholone: DO, drug dose  
fluorometholone: DT, drug therapy  
fluorometholone: TP, topical drug administration  
loteprednol etabonate: DO, drug dose  
loteprednol etabonate: DT, drug therapy  
loteprednol etabonate: TP, topical drug administration  
    **cyclosporin A: DT, drug therapy**  
    **cyclosporin A: TP, topical drug administration**  
    linseed oil: DT, drug therapy  
primrose oil: DT, drug therapy  
theratears  
hydroeyes  
refresh liquigel  
genteal gel

CAS REGISTRY NO.: (doxycycline) 10592-13-9, 17086-28-1, 564-25-0;  
(tetracycline) 23843-90-5, 60-54-8, 64-75-5; (essential  
fatty acid) 11006-87-4; (fluorometholone) 426-13-1;  
(loteprednol etabonate) 82034-46-6; (**cyclosporin**  
**A**) **59865-13-3**, 63798-73-2; (linseed oil)  
8001-26-1; (primrose oil) 65546-85-2  
CHEMICAL NAME: (1) Theratears; (2) Hydroeyes; (3) Refresh liquigel; (4)  
Genteal gel; (5) Alrex; (6) **Restasis**  
COMPANY NAME: (1) Advance vision; (2) Science based health; (4) Novartis;  
(5) Pharmos; (6) Allergan

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ACCESSION NUMBER: 2005405102 EMBASE Full-text  
TITLE: The effects of LASIK on the ocular surface.  
AUTHOR: Solomon R.; Donnenfeld E.D.; Perry H.D.  
CORPORATE SOURCE: Dr. E.D. Donnenfeld, Ophthalmic Consultants of Long Island,  
Rockville Centre, 2000 North Village Avenue, New York, NY  
11570, United States. eddoph@aol.com  
SOURCE: Ocular Surface, (2004) Vol. 2, No. 1, pp. 34-44. .  
Refs: 78  
ISSN: 1542-0124  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
012 Ophthalmology  
017 Public Health, Social Medicine and Epidemiology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 22 Sep. 2005  
Last Updated on STN: 22 Sep 2005

ABSTRACT: Laser in situ keratomileusis (LASIK) can affect corneal sensation, aqueous tear production, wound healing, and the incidence of corneal erosions. Virtually all patients experience dry eye at least transiently after LASIK. Because intact corneal sensation drives tear production, denervation associated with the LASIK procedure is the most significant cause of post-LASIK dry eye. To prevent symptomatic postoperative dry eye, it is crucial to identify and treat pre-existing dry eye before surgery. This review addresses the pathophysiology and management of dry eye, as well as the relationship between LASIK and corneal erosions, and suggests intra- and post-operative management techniques to minimize complications and maximize the stability of the ocular surface. Contraindications to LASIK and alternative refractive surgical procedures are discussed. .COPYRGT.2004 Ethis Communications, Inc. All rights reserved.

CONTROLLED TERM: Medical Descriptors:  
\*keratomileusis  
\*dry eye: CO, complication  
\*dry eye: DI, diagnosis  
\*dry eye: DT, drug therapy  
\*dry eye: ET, etiology  
\*dry eye: PC, prevention  
\*cornea erosion: CO, complication  
\*cornea erosion: ET, etiology  
\*cornea erosion: SU, surgery  
\*cornea erosion: TH, therapy  
tear film  
denervation  
postoperative care  
treatment contraindication  
surgical technique  
risk factor  
preoperative evaluation  
lacrimal fluid  
lacrimation  
drug response  
keratectomy  
human  
clinical trial  
review  
Drug Descriptors:  
artificial tear: CM, drug comparison  
artificial tear: DT, drug therapy  
  cyclosporin A: CT, clinical trial  
  cyclosporin A: CM, drug comparison  
  cyclosporin A: DT, drug therapy  
  cyclosporin A: TP, topical drug administration  
doxycycline: PO, oral drug administration  
methylprednisolone: DT, drug therapy  
omega 3 fatty acid  
icosapentaenoic acid  
docosahexaenoic acid  
  linseed oil: DT, drug therapy  
  linseed oil: PO, oral drug administration  
CAS REGISTRY NO.: (cyclosporin A) 59865-13-3,  
63798-73-2; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0;  
(methylprednisolone) 6923-42-8, 83-43-2; (icosapentaenoic  
acid) 25378-27-2, 32839-30-8; (docosahexaenoic acid)  
25167-62-8, 32839-18-2; (linseed oil) 8001-26-1  
CHEMICAL NAME: (1) Restasis  
COMPANY NAME: (1) Allergan  
L139 ANSWER 31 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights  
reserved on STN  
ACCESSION NUMBER: 2003476197 EMBASE Full-text  
TITLE: The potential of chitosam in ocular drug delivery.  
AUTHOR: Alonso M.J.; Sanchez A.  
CORPORATE SOURCE: M.J. Alonso, Dept. of Pharm./Pharmaceut. Technol., Faculty  
of Pharmacy, University of Santiago de Compostela, 15782  
Santiago de Compostela, Spain. ffmjalon@ucs.es  
SOURCE: Journal of Pharmacy and Pharmacology, (2003) Vol. 55, No.  
11, pp. 1451-1463. .  
Refs: 76  
ISSN: 0022-3573 CODEN: JPPMAB  
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 037 Drug Literature Index  
030 Pharmacology  
039 Pharmacy  
012 Ophthalmology  
052 Toxicology  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 4 Dec 2003  
Last Updated on STN: 4 Dec 2003

ABSTRACT: This paper presents an overview of the potential of chitosan-based systems for improving the retention and biodistribution of drugs applied topically onto the eye. Besides its low toxicity and good ocular tolerance, chitosan exhibits favourable biological behaviour, such as bioadhesion- and permeability-enhancing properties, and also interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. The review summarizes the techniques for the production of chitosan gels, chitosan-coated colloidal systems and chitosan nanoparticles, and describes their mechanism of action upon contact with the ocular mucosa. The results reported until now have provided evidence of the potential of chitosan gels for enhancing and prolonging the retention of drugs on the eye surface. On the other hand, chitosan-based colloidal systems were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal systems containing indometacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticles containing ciclosporin). Finally, the tolerance, toxicity and biodegradation of the carriers under evaluation were reviewed.

CONTROLLED TERM: Medical Descriptors:  
nonhuman  
drug potency  
drug delivery system  
drug retention  
drug distribution  
    **eye disease: DT, drug therapy**  
drug tolerance  
adhesion  
drug penetration  
physical chemistry  
drug design  
drug manufacture  
gel  
colloid  
coated particle  
nanoparticle  
drug mechanism  
evidence based medicine  
eye  
drug transport  
drug accumulation  
cornea epithelium  
conjunctiva epithelium  
biodegradation  
wound healing: DT, drug therapy  
drug dosage form  
drug blood level  
review  
Drug Descriptors:  
\*chitosan: PD, pharmacology  
\*chitosan: PR, pharmaceuticals

\*chitosan: IO, intraocular drug administration  
 \*chitosan: PK, pharmacokinetics  
 \*chitosan: TP, topical drug administration  
 \*chitosan: DT, drug therapy  
 \*chitosan: CB, drug combination  
 \*chitosan: TO, drug toxicity  
 \*chitosan: DO, drug dose  
 \*chitosan: CR, drug concentration  
 \*chitosan: IV, intravenous drug administration  
 \*chitosan: PO, oral drug administration  
 \*chitosan: NA, intranasal drug administration  
 indometacin: PD, pharmacology  
 indometacin: PR, pharmaceuticals  
 indometacin: IO, intraocular drug administration  
 indometacin: PK, pharmacokinetics  
 indometacin: TP, topical drug administration  
 indometacin: DT, drug therapy  
 indometacin: CB, drug combination  
 indometacin: TO, drug toxicity  
 indometacin: DO, drug dose  
 cyclosporin: PD, pharmacology  
 cyclosporin: PR, pharmaceuticals  
 cyclosporin: IO, intraocular drug administration  
 cyclosporin: PK, pharmacokinetics  
     **cyclosporin: TP, topical drug administration**  
 cyclosporin: DT, drug therapy  
 cyclosporin: CB, drug combination  
 cyclosporin: TO, drug toxicity  
 cyclosporin: DO, drug dose  
 n acetylglucosamine: DT, drug therapy  
 n acetylglucosamine: PD, pharmacology  
 n acetylglucosamine: CB, drug combination  
 n acetylglucosamine: PR, pharmaceuticals  
 oligomer: DT, drug therapy  
 oligomer: PD, pharmacology  
 oligomer: CB, drug combination  
 oligomer: PR, pharmaceuticals  
 tobramycin: DT, drug therapy  
 tobramycin: PR, pharmaceuticals  
 tobramycin: CB, drug combination  
 microsphere: CB, drug combination  
 microsphere: PR, pharmaceuticals  
 aciclovir: CB, drug combination  
 aciclovir: PR, pharmaceuticals  
 drug carrier: PD, pharmacology  
 drug carrier: PR, pharmaceuticals  
 drug carrier: IO, intraocular drug administration  
 drug carrier: PK, pharmacokinetics  
 drug carrier: TP, topical drug administration  
 drug carrier: DT, drug therapy  
 drug carrier: CB, drug combination  
 drug carrier: TO, drug toxicity  
 drug carrier: DO, drug dose  
     **macrogol: CB, drug combination**  
     **macrogol: PR, pharmaceuticals**  
 ofloxacin: CB, drug combination  
 ofloxacin: PR, pharmaceuticals  
 ofloxacin: CR, drug concentration  
 liposome: CB, drug combination  
 liposome: PR, pharmaceuticals

idoxuridine: DT, drug therapy  
idoxuridine: CB, drug combination  
idoxuridine: PR, pharmaceuticals  
idoxuridine: PD, pharmacology  
polycaprolactone: CB, drug combination  
polycaprolactone: PR, pharmaceuticals  
diazepam: CB, drug combination  
diazepam: PR, pharmaceuticals  
diazepam: PD, pharmacology  
polylysine: CB, drug combination  
polylysine: PR, pharmaceuticals  
polylysine: PD, pharmacology

CAS REGISTRY NO.: (chitosan) 9012-76-4; (indometacin) 53-86-1, 74252-25-8,  
7681-54-1; (cyclosporin) 79217-60-0; (n acetylglucosamine)  
7512-17-6; (tobramycin) 32986-56-4; (aciclovir) 59277-89-3;  
(macrogol) 25322-68-3; (ofloxacin) 82419-36-1;  
(idoxuridine) 54-42-2; (polycaprolactone) 24980-41-4,  
25248-42-4; (diazepam) 439-14-5; (polylysine) 25104-18-1,  
25988-63-0, 33960-24-6, 38000-06-5, 73565-56-7

L139 ANSWER 32 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002182844 EMBASE Full-text  
TITLE: Current issues in Sjogren's syndrome.  
AUTHOR: Jonsson R.; Moen K.; Vestrheim D.; Szodoray P.  
CORPORATE SOURCE: Dr. R. Jonsson, Broegelmann Research Laboratory, Amauer  
Hansen Building, N-5021 Bergen, Norway.  
roland.jonsson@gades.uib.no  
SOURCE: Oral Diseases, (2002) Vol. 8, No. 3, pp. 130-140. .  
Refs: 132  
ISSN: 1354-523X CODEN: ORDIFD  
COUNTRY: Denmark  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 011 Otorhinolaryngology  
026 Immunology, Serology and Transplantation  
031 Arthritis and Rheumatism  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 6 Jun 2002  
Last Updated on STN: 6 Jun 2002

ABSTRACT: Sjogren's syndrome is a chronic autoimmune and rheumatic disorder with prominent sicca complaints from the mucous membranes because of lack of proper exocrine secretions. There is no straightforward and simple diagnostic test for Sjogren's syndrome, although several classification criteria have been designed including several oral diagnostic tests. A new set of classification criteria in a joint effort by research groups in Europe and USA has recently been presented. A large number of autoantibodies have been reported in Sjogren's syndrome where, in some cases, the antibodies are correlated with the extent and severity of disease. The finding of serum autoantibodies directed against the muscarinic M3 receptor is an important advance in understanding the pathogenesis of not only the impaired glandular function but also associated features of autonomic dysfunction in some patients. The treatment of primary Sjogren's syndrome is still mainly symptomatic.

CONTROLLED TERM: Medical Descriptors:  
\*Sjogren syndrome: DI, diagnosis  
\*Sjogren syndrome: DT, drug therapy  
\*Sjogren syndrome: EP, epidemiology



\*Sjogren syndrome: ET, etiology  
 \*Sjogren syndrome: TH, therapy  
 genetics  
 environmental factor  
 immunopathology: ET, etiology  
 autoimmunity  
 disease classification  
 antibody titer  
 palliative therapy  
 virus infection: ET, etiology  
 bacterial infection: ET, etiology  
 histopathology  
 animal model  
 symptomatology  
 diagnostic test  
 saliva analysis  
 serodiagnosis  
 biopsy  
     dry eye: CO, complication  
     dry eye: DT, drug therapy  
     dry eye: TH, therapy  
 xerostomia: CO, complication  
 xerostomia: DT, drug therapy  
 side effect: SI, side effect  
 disease course  
 human  
 nonhuman  
 review  
 priority journal  
 Drug Descriptors:  
 autoantibody  
 muscarinic receptor  
 artificial tear  
     **ointment base**  
 saliva substitute  
 toothpaste  
 fluoride  
 pilocarpine: DT, drug therapy  
 pilocarpine: PO, oral drug administration  
 alpha interferon: DT, drug therapy  
 quinuclidine derivative: AE, adverse drug reaction  
 quinuclidine derivative: DT, drug therapy  
 cemiveline: AE, adverse drug reaction  
 cemiveline: DT, drug therapy  
 hydroxychloroquine: DT, drug therapy  
 azathioprine: DT, drug therapy  
     **cyclosporin A: DT, drug therapy**  
 cyclophosphamide: DT, drug therapy  
 nonsteroid antiinflammatory agent: DT, drug therapy  
 steroid: DT, drug therapy  
 unclassified drug  
 CAS REGISTRY NO.: (fluoride) 16984-48-8; (pilocarpine) 148-72-1, 54-71-7,  
 92-13-7; (hydroxychloroquine) 118-42-3, 525-31-5;  
 (azathioprine) 446-86-6; (**cyclosporin A**  
 ) **59865-13-3**, 63798-73-2; (cyclophosphamide)  
 50-18-0

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ACCESSION NUMBER: 2002194457 EMBASE Full-text

TITLE: Management of dry eye syndrome.  
 AUTHOR: Lee G.Å.  
 CORPORATE SOURCE: Dr. G.A. Lee, Royal Brisbane Hospital, Brisbane, QLD,  
 Australia  
 SOURCE: Medicine Today, (2002) Vol. 3, No. 5, pp. 87-90. .  
 ISSN: 1443-430X CODEN: MTNBCV  
 COUNTRY: Australia  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 012 Ophthalmology  
 037 Drug Literature Index  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 13 Jun 2002  
 Last Updated on STN: 13 Jun 2002  
 CONTROLLED TERM: Medical Descriptors:  
     \*dry eye: DT, drug therapy  
     \*dry eye: ET, etiology  
     \*dry eye: SU, surgery  
     \*dry eye: TH, therapy  
 tear film  
 symptomatology  
 lacrimation  
 medical assessment  
 anamnesis  
 visual acuity  
 visual system examination  
 Schirmer test  
 conservative treatment  
     lacrimal duct occlusion  
 cauterization  
 diet supplementation  
 ointment  
 human  
 article  
 Drug Descriptors:  
 eye drops: DT, drug therapy  
 eye drops: TP, topical drug administration  
 lubricating agent: DT, drug therapy  
 lubricating agent: TP, topical drug administration  
 carboxymethylcellulose: DT, drug therapy  
 carboxymethylcellulose: TP, topical drug administration  
 artificial tear: DT, drug therapy  
 artificial tear: TP, topical drug administration  
 bion tears: DT, drug therapy  
 bion tears: TP, topical drug administration  
 hydroxypropylmethylcellulose: DT, drug therapy  
 hydroxypropylmethylcellulose: TP, topical drug  
 administration  
 methylcellulose: DT, drug therapy  
 methylcellulose: TP, topical drug administration  
 tears naturale: DT, drug therapy  
 tears naturale: TP, topical drug administration  
 hydroxypropylcellulose: DT, drug therapy  
 hydroxypropylcellulose: TP, topical drug administration  
 omega 3 fatty acid: PD, pharmacology  
 omega 6 fatty acid: PD, pharmacology  
 retinol: DT, drug therapy  
 retinol: PR, pharmaceuticals  
     cyclosporin: DT, drug therapy  
     cyclosporin: PR, pharmaceuticals  
 povidone: DT, drug therapy

povidone: TP, topical drug administration  
 hydroxyethylcellulose: DT, drug therapy  
 hydroxyethylcellulose: TP, topical drug administration  
 hyaluronic acid: DT, drug therapy  
 hyaluronic acid: TP, topical drug administration  
 polyvinyl alcohol: DT, drug therapy  
 polyvinyl alcohol: TP, topical drug administration  
 dextran 70: DT, drug therapy  
 dextran 70: TP, topical drug administration  
 carbomer: DT, drug therapy  
 carbomer: TP, topical drug administration  
   paraffin: DT, drug therapy  
   paraffin: TP, topical drug administration  
   lanolin: DT, drug therapy  
   lanolin: TP, topical drug administration  
 clerz moisturizing drops  
 in a wink moisturizing eyedrops  
 minims artificial tears  
 vismed  
 refresh  
 refresh tears plus  
 genteal lubricant eye drops  
 poly tears  
 liquifilm tears  
 liquifilm forte  
 murine revival eyes  
 murine tears for eyes  
 tears plus  
 poly gel lubricating eye gel  
 geltears  
 viscotears  
 genteal moisturizing eye gel  
 duratears lubricating eye ointment  
 poly visc  
 lacri lube

CAS REGISTRY NO.: (carboxymethylcellulose) 8050-38-2, 9000-11-7, 9004-32-4,  
 9050-04-8; (hydroxypropylmethylcellulose) 9004-65-3;  
 (methylcellulose) 79484-92-7, 9004-67-5;  
 (hydroxypropylcellulose) 9004-64-2; (retinol) 68-26-8,  
 82445-97-4; (cyclosporin) 79217-60-0; (povidone)  
 9003-39-8; (hydroxyethylcellulose) 9004-62-0; (hyaluronic  
 acid) 31799-91-4, 9004-61-9, 9067-32-7; (polyvinyl alcohol)  
 37380-95-3, 9002-89-5; (carbomer) 9007-20-9, 9062-04-8;  
 (lanolin) 70321-63-0, 8006-54-0, 8020-84-6, 8031-44-5,  
 8038-28-6; (lacri lube) 78200-24-5

CHEMICAL NAME: Cellufresh; Clerz moisturizing drops; In a wink  
 moisturizing eyedrops; Minims artificial tears; Bion tears;  
 Vismed; Refresh; Refresh tears plus; Genteal lubricant eye  
 drops; Isopto tears; Methopt; Poly tears; Tears naturale;  
 Liquifilm tears; Liquifilm forte; Murine revival eyes;  
 Murine tears for eyes; Tears plus; Celluvisc; Poly gel  
 lubricating eye gel; Geltears; Viscotears; Genteal  
 moisturizing eye gel; Duratears lubricating eye ointment;  
 Poly visc; Lacri lube; Lacrisert

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ACCESSION NUMBER: 2001319104 EMBASE Full-text

TITLE: Can we still suggest the topical cyclosporin treatment in  
 cutaneous disorders?.

AUTHOR: Vena G.A.; Cassano N.  
CORPORATE SOURCE: G.A. Vena, Istituto Dermopatico dell'Immacolata, I.D.I.,  
IRCCS, via Monti di Creta 104, 00167 Rome, Italy.  
g.vena@dermatologia.uniba.it  
SOURCE: Journal of the European Academy of Dermatology and  
Venereology, (2001) Vol. 15, No. 1, pp. 18-19. .  
Refs: 12  
ISSN: 0926-9959 CODEN: JEAVEQ  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Editorial  
FILE SEGMENT: 012 Ophthalmology  
013 Dermatology and Venereology  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
ENTRY DATE: Entered STN: 4 Oct 2001  
Last Updated on STN: 4 Oct 2001  
CONTROLLED TERM: Medical Descriptors:  
\*skin disease: DM, disease management  
\*skin disease: DT, drug therapy  
immunomodulation  
antiinflammatory activity  
psoriasis: DT, drug therapy  
atopic dermatitis: DT, drug therapy  
contact dermatitis: DT, drug therapy  
guinea pig  
drug formulation  
pyoderma gangrenosum: DT, drug therapy  
relapse  
drug blood level  
eye disease: DT, drug therapy  
drug absorption  
side effect: SI, side effect  
drug cost  
human  
nonhuman  
animal experiment  
animal model  
editorial  
priority journal  
Drug Descriptors:  
\*cyclosporin A: AE, adverse drug reaction  
\*cyclosporin A: AD, drug administration  
\*cyclosporin A: CR, drug concentration  
\*cyclosporin A: DT, drug therapy  
\*cyclosporin A: PE, pharmacoeconomics  
\*cyclosporin A: PR, pharmaceuticals  
\*cyclosporin A: PK, pharmacokinetics  
\*cyclosporin A: IL, intralesional drug administration  
\*cyclosporin A: PO, oral drug administration  
\*cyclosporin A: TP, topical drug administration  
petrolatum  
CAS REGISTRY NO.: (cyclosporin A) 59865-13-3, 63798-73-2; (petrolatum)  
8009-03-8

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ACCESSION NUMBER: 2000389759 EMBASE Full-text  
TITLE: Mooren's ulcer in China: A study of clinical

characteristics and treatment.  
AUTHOR: Chen J.; Xie H.; Wang Z.; Yang B.; Liu Z.; Chen L.; Gong X.; Lin Y.  
CORPORATE SOURCE: Dr. J. Chen, Zhongshan Ophthalmic Center, Sun Yat-sen Univ. of Medical Sci., Guangzhou 510060 PR, China.  
zoc@gzsums.edu.cn  
SOURCE: British Journal of Ophthalmology, (2000) Vol. 84, No. 11, pp. 1244-1249. .  
Refs: 17  
ISSN: 0007-1161 CODEN: BJOPAL  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 012 Ophthalmology  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 27 Nov 2000  
Last Updated on STN: 27 Nov 2000

ABSTRACT: Aims-To investigate the clinical characteristics and compare the effects of several methods of treatment of Mooren's corneal ulcer. Methods-550 consecutive cases of Mooren's corneal ulcer were analysed in patients, including age, sex, laterality of eye, ulcer location, perforative rate, cure rate of surgeries, recurrent rate, the effects of conjunctiva excision, lamellar keratoplasty (LKP), and LKP plus 1% cyclosporin A eye drops. Results-The average age of onset was 48.4 years of age. The ratio of males to females was 1:0.74. 165 (30%) cases had the disease bilaterally, of which 52 (31.5%) occurred in the young age group and 113 (68.5%) in the old age group. Ulcers of 501 eyes (70.1%) were located at the limbus of the palpebral fissure. The perforation rate was 13.3%, with perforation of 41 eyes (43.2%) occurring in the young age group and 54 (56.8%) in the old age group. Post-operative recurrence rate was 25.6%. The cure rate of the first procedure of LKP plus 1% cyclosporin A eye drops was 73.7%. The final cure rate was 95.6%, and the postoperative preservation rate of the eye globe was 99.7%. Conclusion-This primary study provided the clinical characteristics of patients with Mooren's corneal ulcer in China. LKP plus 1% \*\*\*cyclosporin.\*\*\* A eye drops was an effective treatment.

CONTROLLED TERM: Medical Descriptors:  
\*cornea rodent ulcer: DT, drug therapy  
\*cornea rodent ulcer: SU, surgery  
China  
clinical feature  
cornea ulcer: DT, drug therapy  
cornea ulcer: SU, surgery  
cornea perforation: DT, drug therapy  
cornea perforation: SU, surgery  
treatment outcome  
recurrence risk  
conjunctiva disease: SU, surgery  
keratoplasty  
onset age  
sex difference  
age  
cornea limbus  
eyelid  
recurrent disease  
drug efficacy  
eye surgery  
postoperative period

human  
male  
female  
major clinical study  
clinical trial  
controlled study  
human tissue  
adolescent  
aged  
adult  
article  
priority journal  
Drug Descriptors:

\*cyclosporin A: CT, clinical trial  
\*cyclosporin A: DT, drug therapy  
\*cyclosporin A: PD, pharmacology  
\*cyclosporin A: TP, topical drug administration  
eye drops: CT, clinical trial  
eye drops: DT, drug therapy  
eye drops: PD, pharmacology  
eye drops: TP, topical drug administration  
antistreptolysin: EC, endogenous compound  
rheumatoid factor: EC, endogenous compound  
antinuclear antibody: EC, endogenous compound  
olive oil  
prednisolone: CT, clinical trial  
prednisolone: DT, drug therapy  
prednisolone: PD, pharmacology  
prednisolone: TP, topical drug administration  
dexamethasone: CT, clinical trial  
dexamethasone: DT, drug therapy  
dexamethasone: PD, pharmacology  
dexamethasone: TP, topical drug administration  
antibiotic agent: CT, clinical trial  
antibiotic agent: TP, topical drug administration  
immunosuppressive agent: CT, clinical trial  
immunosuppressive agent: DT, drug therapy  
immunosuppressive agent: PD, pharmacology  
immunosuppressive agent: TP, topical drug administration  
CAS REGISTRY NO.: (cyclosporin A) 59865-13-3,  
63798-73-2; (antistreptolysin) 9006-92-2; (rheumatoid  
factor) 9009-79-4; (olive oil) 8001-25-0; (prednisolone)  
50-24-8; (dexamethasone) 50-02-2  
COMPANY NAME: Sandoz (Switzerland)

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ACCESSION NUMBER: 97232229 EMBASE Full-text

DOCUMENT NUMBER: 1997232229

TITLE: [Cyclosporine effect in corneal neovascularization].

EFECTO DE LA CICLOSPORINA SOBRE LA NEOVASCULARIZATION CORNEAL.

AUTHOR: OShea C.G.; Cuevas-Cancino O.; Naranjo-Tackman R.; Ozorno-Zarate J.

SOURCE: Revista Mexicana de Oftalmologia, (1997) Vol. 71, No. 2, pp. 41-43. .

Refs: 14

ISSN: 0187-4519 CODEN: RMOFEM

COUNTRY: Mexico

DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 012 Ophthalmology  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: Spanish  
SUMMARY LANGUAGE: English; Spanish  
ENTRY DATE: Entered STN: 4 Sep 1997  
Last Updated on STN: 4 Sep 1997

ABSTRACT: Human and animal investigations since the mid 1970's have demonstrated the effectiveness of **cyclosporine** (CsA) as an immunosuppressed agent. We sought to determine if **cyclosporine** could suppress Corneal Neovascularization induced by interleukin-2. Forty laboratory mice were treated with daily IM injections of **cyclosporine** (25 mg/kg in olive oil) for 3 days before and 2 weeks following the intrastromal injections of 0.5/ $\mu$ l (5 IU) mouse interleukin-2. The animals in the control group received IM injections of olive oil. The mean area of corneal neovascularization 4, 8 and 12 weeks after injections was 9.2, 9.1 and 9.2 mm<sup>2</sup> respectively, in controls and 4.9, 5.3 and 5.2 mm<sup>2</sup> in **cyclosporine** treated mice (P < 0.02; T students test). **Cyclosporine** causes a significant reduction in IL-2 induced Corneal Neovascularization that may, in part account for its ability to prolong corneal allograft survival especially in the high risk patient.

CONTROLLED TERM: Medical Descriptors:  
\*cornea neovascularization: PC, prevention  
animal experiment  
animal model  
article  
controlled study  
cornea transplantation  
graft survival  
intramuscular drug administration  
mouse  
nonhuman  
Drug Descriptors:  
\*cyclosporin  
\*interleukin 2  
\*olive oil

CAS REGISTRY NO.: (cyclosporin) 79217-60-0; (interleukin 2)  
85898-30-2; (olive oil) 8001-25-0

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ACCESSION NUMBER: 96152238 EMBASE Full-text  
DOCUMENT NUMBER: 1996152238  
TITLE: Effects of **cyclosporin A** on the induction of oral tolerance.  
AUTHOR: Fukushima A.; Whitcup S.M.; Nussenblatt R.B.; Gery I.  
CORPORATE SOURCE: Laboratory of Immunology, National Eye Institute, Bethesda, MD 20892-1858, United States  
SOURCE: Annals of the New York Academy of Sciences, (1996) Vol. 778, pp. 376-378. .  
ISSN: 0077-8923 CODEN: ANYAA  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 012 Ophthalmology  
026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English

ENTRY DATE: Entered STN: 4 Jun 1996  
Last Updated on STN: 4 Jun 1996  
CONTROLLED TERM: Medical Descriptors:  
\*immunological tolerance  
\*uveitis  
animal cell  
animal experiment  
animal model  
article  
autoimmunity  
controlled study  
immunization  
lymphocyte proliferation  
male  
nonhuman  
rat  
Drug Descriptors:  
\*cyclosporin a  
\*retina s antigen  
immunosuppressive agent  
olive oil  
CAS REGISTRY NO.: (cyclosporin a) 59865-13-3,  
63798-73-2; (retina s antigen) 113315-03-0; (olive oil)  
8001-25-0

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ACCESSION NUMBER: 94311888 EMBASE Full-text  
DOCUMENT NUMBER: 1994311888  
TITLE: Topical **cyclosporin** treatment of keratoconjunctivitis sicca in secondary Sjogren's syndrome.  
AUTHOR: Gunduz K.; Ozdemir O.  
CORPORATE SOURCE: Department of Ophthalmology, Faculty of Medicine, University of Ankara, Ankara, Turkey  
SOURCE: Acta Ophthalmologica, (1994) Vol. 72, No. 4, pp. 438-442. . ISSN: 0001-639X CODEN: ACOPAT  
COUNTRY: Denmark  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 012 Ophthalmology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 27 Oct 1994  
Last Updated on STN: 27 Oct 1994

ABSTRACT: Topical **cyclosporin** 2% in olive oil was investigated for its possible immunoregulatory role on the dry eye state in patients with secondary Sjogren's syndrome. The study was a randomized, double-masked, placebo-controlled trial. Thirty eyes of 15 patients were randomized to undergo treatment with topical cyclosporin in olive oil and 30 eyes of the other 15 patients received a placebo, which was the sterile olive oil used as a vehicle for the **cyclosporin**. The effect of the 2-month long treatment with either medication on the status of the dry eye state was measured by Schirmer-I test, tear film break-up time and rose bengal staining. There was a significant increase in the break-up time and a significant decrease in rose bengal staining score between the **cyclosporin** and control groups at the end of the 2-month study period ( $p < 0.01$ ) Schirmer-I test remained unaffected ( $p > 0.05$ ). These results probably indicate that topical **cyclosporin** modulates the goblet cell function in secondary Sjogren's associated keratoconjunctivitis sicca and through this mucus enhancing action or some other mechanism not yet known, helps to maintain the



structural integrity of the epithelium.

CONTROLLED TERM: Medical Descriptors:  
\*keratoconjunctivitis sicca: CN, congenital disorder  
\*keratoconjunctivitis sicca: ET, etiology  
\*keratoconjunctivitis sicca: DT, drug therapy  
\*sjogren syndrome: ET, etiology  
\*sjogren syndrome: CN, congenital disorder  
adult  
article  
clinical article  
clinical trial  
controlled study  
double blind procedure  
dry eye: ET, etiology  
dry eye: DT, drug therapy  
dry eye: CN, congenital disorder  
female  
human  
immunoregulation  
male  
randomized controlled trial  
staining  
tear film  
topical drug administration  
Drug Descriptors:  
\*cyclosporin: CT, clinical trial  
\*cyclosporin: AD, drug administration  
\*cyclosporin: DT, drug therapy  
\*cyclosporin: PD, pharmacology  
cyclosporin a: CT, clinical trial  
cyclosporin a: AD, drug administration  
cyclosporin a: DT, drug therapy  
cyclosporin a: PD, pharmacology  
olive oil  
placebo  
rose bengal  
CAS REGISTRY NO.: (cyclosporin) 79217-60-0; (cyclosporin a) 59865-13-3, 63798-73-2; (olive oil) 8001-25-0; (rose bengal) 11121-48-5, 11139-83-6, 632-68-8

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ACCESSION NUMBER: 94073961 EMBASE Full-text  
DOCUMENT NUMBER: 1994073961  
TITLE: New approaches to dry-eye therapy.  
AUTHOR: Tsubota K.  
CORPORATE SOURCE: 5-11-13 Sugano, Ichikawa, Chiba 272, Japan  
SOURCE: International Ophthalmology Clinics, (1994) Vol. 34, No. 1, pp. 115-128. .  
ISSN: 0020-8167 CODEN: IOPCAV  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 012 Ophthalmology  
027 Biophysics, Bioengineering and Medical Instrumentation  
037 Drug Literature Index  
LANGUAGE: English  
ENTRY DATE: Entered STN: 30 Mar 1994

Last Updated on STN: 30 Mar 1994  
 CONTROLLED TERM: Medical Descriptors:  
     \*dry eye: TH, therapy  
     \*dry eye: DT, drug therapy  
 clinical trial  
 evaporation  
 eyelid reflex  
 human  
 lacrimal fluid  
 lacrimation  
 moisture  
 priority journal  
 review  
     sjoegren syndrome: TH, therapy  
     sjoegren syndrome: DT, drug therapy  
 spectacles  
 Drug Descriptors:  
     \*artificial tear: DT, drug therapy  
     \*artificial tear: PD, pharmacology  
     5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: DT,  
     drug therapy  
     5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: PD,  
     pharmacology  
     aldehyde reductase: EC, endogenous compound  
     alpha interferon: DT, drug therapy  
     alpha interferon: PD, pharmacology  
     arachis oil: PD, pharmacology  
     arachis oil: DT, drug therapy  
     arginylglycylaspartic acid: DT, drug therapy  
     arginylglycylaspartic acid: PD, pharmacology  
     cyclosporin a: PD, pharmacology  
     cyclosporin a: DT, drug therapy  
     dextran derivative: PD, pharmacology  
     dextran derivative: DT, drug therapy  
     epalrestat  
     epidermal growth factor: PD, pharmacology  
     epidermal growth factor: DT, drug therapy  
     fibronectin: EC, endogenous compound  
     hyaluronic acid: DT, drug therapy  
     hyaluronic acid: PD, pharmacology  
     hydroxypropylmethylcellulose: PD, pharmacology  
     hydroxypropylmethylcellulose: DT, drug therapy  
     retinoic acid: DT, drug therapy  
     retinoic acid: PD, pharmacology  
     retinol: PD, pharmacology  
     retinol: DT, drug therapy  
     tsukubaenolide: PD, pharmacology  
     tsukubaenolide: DT, drug therapy  
     visco tears  
     unclassified drug  
 CAS REGISTRY NO.: (5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione)  
 79714-31-1; (aldehyde reductase) 58591-34-7, 9023-11-4,  
 9028-31-3; (arachis oil) 8002-03-7, 8031-20-7;  
 (arginylglycylaspartic acid) 99896-85-2; (  
 cyclosporin a) 59865-13-3,  
 63798-73-2; (epalrestat) 82159-09-9; (epidermal growth  
 factor) 62229-50-9; (fibronectin) 86088-83-7; (hyaluronic  
 acid) 31799-91-4, 9004-61-9, 9067-32-7;  
 (hydroxypropylmethylcellulose) 9004-65-3; (retinoic acid)  
 302-79-4; (retinol) 68-26-8, 82445-97-4; (tsukubaenolide)

104987-11-3

CHEMICAL NAME: (1) Ct 112; (2) Kinedak; (3) Visco tears; Fk 506  
COMPANY NAME: (1) Senju pharmaceutical (Japan); (2) Ono (Japan); (3)  
Alcon (United States)

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ACCESSION NUMBER: 94116169 EMBASE Full-text  
DOCUMENT NUMBER: 1994116169  
TITLE: Collagen-based drug delivery and artificial tears.  
AUTHOR: Kaufman H.E.; Steinemann T.L.; Lehman E.; Thompson H.W.;  
Varnell E.D.; Jacob- Labarre J.T.; Gebhardt B.M.  
CORPORATE SOURCE: LSU Eye Center, 2020 Gravier Street, New Orleans, LA 70112,  
United States  
SOURCE: Journal of Ocular Pharmacology, (1994) Vol. 10, No. 1, pp.  
17-27. .  
ISSN: 8756-3320 CODEN: JOPHER  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 012 Ophthalmology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 18 May 1994  
Last Updated on STN: 18 May 1994

ABSTRACT: For patients with conditions requiring chronic rather than acute therapy, the advantages of collagen shields in providing high and sustained levels of drugs and/or lubricants to the cornea are outweighed by the difficulty of insertion of the shield and the problem of blurred vision. We have developed a delivery system in which collagen pieces suspended in a viscous vehicle can be instilled into the lower forniceal space, thereby simplifying application and reducing blurring of vision. The collagen pieces (Collasomes) can be formulated with various constituents such as antibiotics or \*\*\*cyclosporine\*\*\*, or with chemical alterations such as the inclusion of a lipid (Lacrisomes) for the treatment of dry eyes. In the normal eyes of volunteers, Collasomes hydrated in a solution of sodium fluorescein and suspended in a methylcellulose vehicle as a model for delivery of water-soluble drugs produced fluorescein concentrations 17 to 42 times higher in the cornea and 6 to 8 times higher in the aqueous humor, compared with fluorescein-containing vehicle alone. In a preliminary controlled study, 76% of patients with moderately severe keratoconjunctivitis sicca (KCS) preferred Lacrisomes to the vehicle control because of a more soothing effect and longer duration of comfort. All preparations were well tolerated by all study subjects. Current studies involve improving drug delivery by chemically modifying the collagen molecule to slow diffusion of the drug from the Collasome matrix, as well as varying the amount of cetyl alcohol and combining it with modified collagen in Lacrisomes to maximize comfort in patients with dry eyes.

CONTROLLED TERM: Medical Descriptors:  
\*dry eye: DT, drug therapy  
\*dry eye: DI, diagnosis  
\*keratoconjunctivitis sicca: DT, drug therapy  
\*keratoconjunctivitis sicca: DI, diagnosis  
adult  
aged  
clinical article  
clinical trial

conference paper  
controlled study  
double blind procedure  
drug bioavailability  
drug tolerance  
female  
foreign body: SI, side effect  
human  
male  
    **photophobia: SI, side effect**  
randomized controlled trial  
    **visual impairment: SI, side effect**  
drug delivery system  
Drug Descriptors:  
\*artificial tear: DT, drug therapy  
\*artificial tear: PR, pharmaceuticals  
\*artificial tear: AE, adverse drug reaction  
\*collagen  
duolube  
eye drops  
fluorescein  
fluorescein sodium  
hexadecanol  
methyl paraben  
methylcellulose  
murocel  
    **petrolatum**  
propyl paraben  
unclassified drug

CAS REGISTRY NO.: (collagen) 9007-34-5; (fluorescein) 2321-07-5, 91316-42-6;  
(fluorescein sodium) 518-47-8; (hexadecanol) 29354-98-1,  
36653-82-4, 51260-59-4; (methyl paraben) 99-76-3;  
(methylcellulose) 79484-92-7, 9004-67-5; (petrolatum)  
8009-03-8; (propyl paraben) 94-13-3  
CHEMICAL NAME: (1) Murocel; (2) Duolube  
COMPANY NAME: (2) Bausch and lomb (United States)

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ACCESSION NUMBER: 92021561 EMBASE Full-text  
DOCUMENT NUMBER: 1992021561  
TITLE: [Sjogren syndrome: Current therapy].  
LA SINDROME DI SJOEGREN: ATTUALITA TERAPEUTICHE.  
AUTHOR: Di Giacinto G.; Piergiacomi G.  
CORPORATE SOURCE: Cattedra di Reumatologia, Universita degli Studi, Piazza  
Roma 22, 60128 Ancona, Italy  
SOURCE: Clinica Terapeutica, (1991) Vol. 139, No. 3-4, pp. 81-92.  
ISSN: 0009-9047 CODEN: CLTEA4  
COUNTRY: Italy  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 003 Endocrinology  
006 Internal Medicine  
011 Otorhinolaryngology  
026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: Italian  
SUMMARY LANGUAGE: English; Italian  
ENTRY DATE: Entered STN: 20 Mar 1992

CONTROLLED TERM:

Last Updated on STN: 20 Mar 1992

Medical Descriptors:

\*disease severity

\*sjoegren syndrome: DT, drug therapy

\*sjoegren syndrome: TH, therapy

\*sjoegren syndrome: SU, surgery

anorexia: SI, side effect

chewing gum

diet

drug efficacy

human

intramuscular drug administration

intranasal drug administration

intravenous drug administration

kidney failure: SI, side effect

leukemia: SI, side effect

mouth ulcer: SI, side effect

nausea: SI, side effect

oral drug administration

rash: SI, side effect

rectal drug administration

review

topical drug administration

vomiting: SI, side effect

**xerophthalmia**

therapy

drug therapy

Drug Descriptors:

\*antiinflammatory agent: AE, adverse drug reaction

\*antiinflammatory agent: DT, drug therapy

\*artificial tear: PR, pharmaceuticals

\*artificial tear: DT, drug therapy

\*corticosteroid: DT, drug therapy

\*hydroxychloroquine: DT, drug therapy

\*hydroxychloroquine: AE, adverse drug reaction

\*immunosuppressive agent: AE, adverse drug reaction

\*immunosuppressive agent: DT, drug therapy

acetylcysteine: DT, drug therapy

anethole trithione: AE, adverse drug reaction

anethole trithione: DT, drug therapy

antihistaminic agent: PD, pharmacology

antihistaminic agent: DT, drug therapy

antihypertensive agent: PD, pharmacology

antihypertensive agent: DT, drug therapy

azathioprine: PD, pharmacology

azathioprine: DT, drug therapy

benzalkonium chloride: DT, drug therapy

bromhexine: PD, pharmacology

bromhexine: DT, drug therapy

carbomer: DT, drug therapy

carboxymethylcellulose: DT, drug therapy

chlorambucil: DT, drug therapy

clonidine: PD, pharmacology

clonidine: DT, drug therapy

cortisone: DT, drug therapy

cyclophosphamide: AE, adverse drug reaction

cyclophosphamide: DT, drug therapy

**cyclosporin: AE, adverse drug reaction**

**cyclosporin: DT, drug therapy**

**cyclosporin a**

dacriosol  
dextran: DT, drug therapy  
fibronectin: DT, drug therapy  
gelatin: DT, drug therapy  
glycosaminoglycan polysulfate: DT, drug therapy  
gold: DT, drug therapy  
hydroxymethylcellulose: DT, drug therapy  
hydroxypropylcellulose: DT, drug therapy  
    **macrogol: DT, drug therapy**  
methotrexate: DT, drug therapy  
methotrexate: PD, pharmacology  
nandrolone decanoate: DT, drug therapy  
nonsteroid antiinflammatory agent: DT, drug therapy  
penicillamine: DT, drug therapy  
penicillamine: AE, adverse drug reaction  
pentosan polysulfate  
phenothiazine derivative: DT, drug therapy  
phenothiazine derivative: PD, pharmacology  
polyacrylic acid  
polyvinyl alcohol: DT, drug therapy  
propyl paraben: DT, drug therapy  
retinol: PD, pharmacology  
retinol: DT, drug therapy  
sorbitol: DT, drug therapy  
tricyclic antidepressant agent: DT, drug therapy  
tricyclic antidepressant agent: PD, pharmacology  
xerotin  
unclassified drug

CAS REGISTRY NO.: (hydroxychloroquine) 118-42-3, 525-31-5; (acetylcysteine) 616-91-1; (anethole trithione) 532-11-6; (azathioprine) 446-86-6; (benzalkonium chloride) 66331-30-4, 78244-97-0, 81181-32-0; (bromhexine) 3572-43-8, 611-75-6; (carbomer) 9007-20-9, 9062-04-8; (carboxymethylcellulose) 8050-38-2, 9000-11-7, 9004-32-4, 9050-04-8; (chlorambucil) 305-03-3; (clonidine) 4205-90-7, 4205-91-8, 57066-25-8; (cortisone) 53-06-5; (cyclophosphamide) 50-18-0; (**cyclosporin**) 79217-60-0; (**cyclosporin a**) **59865-13-3**, 63798-73-2; (dextran) 87915-38-6, 9014-78-2; (fibronectin) 86088-83-7; (gelatin) 9000-70-8; (glycosaminoglycan polysulfate) 63449-40-1; (gold) 7440-57-5; (hydroxymethylcellulose) 37353-59-6; (hydroxypropylcellulose) 9004-64-2; (macrogol) 25322-68-3; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (nandrolone decanoate) 360-70-3; (penicillamine) 2219-30-9, 52-67-5; (pentosan polysulfate) 116001-96-8, 37300-21-3, 37319-17-8; (polyacrylic acid) 74350-43-9, 87003-46-1, 9003-01-4, 9003-04-7; (polyvinyl alcohol) 37380-95-3, 9002-89-5; (propyl paraben) 94-13-3; (retinol) 68-26-8, 82445-97-4; (sorbitol) 26566-34-7, 50-70-4, 53469-19-5

CHEMICAL NAME: (1) Plaquenil; (2) Pemine; (3) **Sandimmune**; (4) Imuran; (5) Methotrexate; (6) Endoxan asta; (7) Linfolysin; (8) Bisolvon; (9) Lacrinorm; (10) Xerotin; (11) Dacriosol; Elmiron; Deca durabolin

COMPANY NAME: (1) Winthrop; (2) Lilly; (3) Sandoz; (4) Burroughs wellcome; (5) Cyanamid; (6) Schering; (7) Istituto sieroterapico milanese; (8) Boehringer; (9) Farmigea; (11) Alcon

L139 ANSWER 42 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 1  
 ACCESSION NUMBER: 2006-284509 [29] WPIX  
 DOC. NO. CPI: C2006-092768  
 TITLE: Gel composition for treating ocular disease, includes hydrophilic polymer, hydrophobic ocular agent, and gelling component.  
 DERWENT CLASS: A18 A23 A25 A96 B07  
 INVENTOR(S): JASTI, B R; LI, X; MAHALINGAM, R  
 PATENT ASSIGNEE(S): (FORM-N) FORMUREX INC  
 COUNTRY COUNT: 112  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2006039558	A2	20060413	(200629)*	EN	40	A61K009-14	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006039558	A2	WO 2005-US35311	20050929

PRIORITY APPLN. INFO: US 2004-617453P 20041009  
 INT. PATENT CLASSIF.:

MAIN: A61K009-14

BASIC ABSTRACT:

WO2006039558 A UPAB: 20060505

NOVELTY - A gel composition comprises a hydrophilic polymer, a hydrophobic ocular agent, and a gelling component. It comprises a gel in an ocular environment and provides a sustained release of the hydrophobic ocular agent from the gel in the ocular environment.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of forming an ocular gel comprising selecting an ocular agent for use in treating an ocular disease; mixing an oil in water to create an oil-in-water emulsion comprising the ocular agent and a non-ionic hydrophilic emulsifier; combining the oil-in-water emulsion with a previously formulated gel comprising a gelling component from hydroxypropylmethylcellulose, hydroxypropylethylcellulose, methylcellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid, xanthan gum, guar gum, locust bean gum, and/or karaya gum carboxyvinyl polymers.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - The composition is used for treating ocular disease by administering the composition to an ocular environment of a subject (claimed). The ocular disease comprises keratoconjunctivitis sicca, conjunctivitis and other ocular allergic responses, dry eye, lysosomal storage diseases, glycogen storage diseases, disorders of collagen, disorders of glycosaminoglycans and proteoglycans, sphingolipidoses, mucopolipidoses, disorders of amino acid metabolism, dysthyroid eye diseases, anterior and posterior corneal

dystrophies, retinal photoreceptor disorders, corneal ulceration, and other ocular wounds such as those following surgery.

ADVANTAGE - The invention can improve the precorneal residence of ophthalmic agents, improve the fraction of drug absorbed by the ocular tissues, and minimize the nasolachrymal drainage, systemic absorption of agents, and associated adverse effects. It provides improved agent loading and delivery properties to the corneal surface. It also provides enhanced solubility, stability, and sustained release of desired agents.

DESCRIPTION OF DRAWING(S) - The figure is a scanning electron micrograph showing the physical stability of an oil phase containing a pharmaceutical agent in an E-Gel. Dwg.1/4

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; GI; DCN  
MANUAL CODES: CPI: A12-V01; B04-B01C1; B04-C01H; B04-C02A; B04-C02B;  
B04-C02D; B04-C03; B04-H19; B12-M02G; B12-M10A4;  
B12-M12H; B14-N03  
TECH UPTX: 20060505

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Component: The hydrophobic ocular agent comprises **cyclosporine A**, and/or protein. The composition comprises a molecular dispersion of the hydrophobic ocular agent. The composition comprises a peanut oil. The molecular dispersion comprises molecules, microparticles, and/or controlled volumes. Preferred Method: An additional agent is administered to provide a combination therapy for the subject.

TECHNOLOGY FOCUS - POLYMERS - Preferred Component: The hydrophilic polymer comprises a poly(alkylene glycol) or a non-ionic hydrophilic **emulsifier**. The poly(alkylene glycol) comprises poly(ethylene glycol). The non-ionic hydrophilic **emulsifier** comprises polyoxyethylene sorbitan monooleate. The gelling component comprises a component from hydroxypropylmethylcellulose, hydroxypropylethylcellulose, methylcellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid, xanthan gum, guar gum, locust bean gum, and/or karaya gum carboxyvinyl polymers. It comprises carboxypolymethylene. The hydrophilic polymer comprises a component from poly(ethylene glycol) (PEG); PEG-caprolactone; PEG-D,L-lactide; poly(ethylene glycol-co-propylene oxide); poly(vinyl alcohol); poly((2-hydroxyethyl)methacrylate); poly(vinyl pyrrolidone); poly(butylene terephthalate-co-ethylene glycol); poly(alkylene oxalates); poly(vinyl alcohols); pluronic acid; sulfonated polystyrene; dextran; dextrin; fibrin, fibrinogen, cellulose, starch, collagen, and/or heparin and hyaluronic acid.

L139 ANSWER 43 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2006-077857 [08] WPIX  
DOC. NO. CPI: C2006-027935  
TITLE: Use of an **emulsion** and optionally an active ingredient to treat **eye** disease and intraocular conditions e.g. intraocular inflammation, infection, cancerous growth, tumors, retinal edema, macular edema and diabetic retinopathy.  
DERWENT CLASS: B04 B05 D16  
INVENTOR(S): BEHAR-COHAN, F; BENITA, S; COUVREUR, P; DE KOZAK, Y; DUBERNET, C; LAMBERT, G; RABINOVICH-GUILLAT, L; BEHAR-COHEN, F; RABINOVICH-GUILLAT, L; DE KOSAK, Y  
PATENT ASSIGNEE(S): (CNRS) CNRS CENT NAT RECH SCI; (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (NOVA-N) NOVAGALI PHARMA SA; (YISS) YISSUM RES DEV CO HEBREW UNIV JERUSALEM; (BEHA-I) BEHAR-COHEN F; (BENI-I) BENITA S; (COUV-I) COUVREUR P; (DKOZ-I) DE KOZAK Y; (DUBE-I) DUBERNET C; (LAMB-I)



LAMBERT G; (RABI-I) RABINOVICH-GUILATT L

COUNTRY COUNT: 112  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2006002963	A1	20060105	(200608)*		9	A61K048-00	
EP 1611879	A1	20060104	(200608)	EN		A61K009-107	
	R:	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR					
WO 2006003519	A2	20060112	(200608)	EN		A61K009-00	
	RW:	AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
	W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006002963	A1	US 2004-891452	20040715
EP 1611879	A1	EP 2004-291684	20040702
WO 2006003519	A2	WO 2005-IB2317	20050701

PRIORITY APPLN. INFO: EP 2004-291684 20040702  
INT. PATENT CLASSIF.:

MAIN: A61K009-00; A61K009-107; A61K048-00  
SECONDARY: A61K031-4738; A61K031-4745; A61K031-70; A61K038-18; A61K038-19; A61K038-20; A61K038-21

BASIC ABSTRACT:

US2006002963 A UPAB: 20060201

NOVELTY - Treating **eye** diseases by injecting intraocularly or periocularly a composition (I) comprising an **emulsion** and optionally at least an active ingredient, is new.

ACTIVITY - Ophthalmological; Antiinflammatory; Cytostatic; Antidiabetic; Virucide.

MECHANISM OF ACTION - None given.

USE - (I) is useful for treating **eye** disease, and intraocular conditions such as intraocular inflammation, infection, cancerous growth, tumors, neo vessel growth originating from the retina and/or from the choroids, retinal edema, macular edema, diabetic retinopathy, retinopathy of prematurity, degenerative diseases of the retina (macular degeneration, retinal dystrophies), **retinal diseases** associated with glial proliferation, ocular conditions such as glaucoma, proliferative **vitreoretinopathy**, diabetic retinopathy, age-related macular degeneration, uveitis, cytomegalovirus retinitis, herpes simplex viral retinal dystrophies, age related macular degeneration (claimed).

The ability of (I) to treat ocular inflammation was assessed. The results showed that (I) exhibited a significant probability value of less than 0.05.  
Dwg.0/2

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: B02-A; B02-B; B02-C01; B02-C02; B02-D; B02-E; B02-M; B02-N; B02-P; B02-R; B02-T; B04-B01B; B04-B03C; B04-C01H; B04-C02E1; B04-E01; B04-E07A; B04-E07C;

B04-E08; B04-G01; B04-G21; B04-G22; B04-H01;  
B04-H02B; B04-H05; B04-H06; B04-H07; B04-H08;  
B04-J03A; B04-J04B; B04-L04C; B04-L05C; B04-N04;  
B04-N06; B05-A03B; B05-B01J; B06-H; B07-H; B08-D01;  
B10-A09B; B10-A10; B10-A12C; B10-A13D; B10-A19;  
B10-B01A; B10-B02A; B10-B02B; B10-B03B; B10-C03;  
B10-C04C; B10-D03; B10-G02; B10-H02E; B12-M02G;  
**B12-M03**; B12-M12C; B14-A01; B14-A02;  
B14-A04; B14-H01L; B14-N03; D05-H11

TECH

UPTX: 20060201

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The

**emulsion** is an oil/water type **emulsion** or hydrogels. The active ingredient is anaesthetics. The **emulsion** is anionic or cationic **emulsions**. The cationic/anionic **emulsion** is an oil/water type **emulsion**

comprising colloid particles having an oily core surrounded by an interfacial film comprising surface active agents and/or lipids; where in the **emulsions** at least part of the surface active agents or lipids in the interfacial film have positively/negatively charged polar groups and the colloid particles have a positive/negative zeta potential respectively). The cationic/anionic **emulsion** comprises (in %w/w): oily carrier (0.5-20 (preferably 0.5-10)%), cationic surfactants or lipids (0.01-2 preferably (0.02-0.4)%) and optionally a non-ionic surfactant (0.05-3 (preferably 0.1-2)%). The **emulsion** comprises phospholipids (0.05-3 (preferably 0.1-2)%). The pH of the **emulsion** is 4-8.5 (preferably 6-8).

The **emulsion** further comprises additive such as osmotic pressure regulators, anti-oxidants, preservatives, dextrose, carriers, stabilizing agents, wetting agents, viscosity enhancers analgesics, cell transport/mobility impending agents such as colchicines, vincristine, cytochalasin B and related compounds; carbonic anhydrase inhibitors such as acetazolamide, methazolamide, dichlorphenamide, diamox and neuroprotectants such as nimodipine and related compounds; antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalixin, oxytetracycline, chloramphenicol, rifampicin, ciprofloxacin, aminosides, gentamycin, erythromycin and penicillin, quinolone, ceftazidime, vancomycin imipeneme; antifungals such as amphotericin B, fluconazole, ketoconazole and miconazole; antibacterials such as sulfonamides, sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals such as idoxuridine, trifluorothymidine, trifluorouridine, acyclovir, ganciclovir, cidofovir, interferon, didanosine (DDI), zidovudine (AZT), foscarnet, vidarabine, irbavirin, protease inhibitors and anti-cytomegalovirus agents; antiallergenics such as sodium cromoglycate, antazoline, methapyriline, chlorpheniramine, cetirizine, pyrilamine and propenpyridamine; synthetic glucocorticoids and mineralocorticoids, hormones forms derivating from the cholesterol metabolism (dehydroepiandrosterone (DHEA), progesterone, estrogens); non-steroidal anti-inflammatories such as salicylate, indomethacin, ibuprofen, diclofenac, flurbiprofen, piroxicam and cyclooxygenase 2 (COX2) inhibitors; antineoplastics such as carmustine, cisplatin, fluorouracil; adriamycin, asparaginase, azacitidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cyclophosphamide, **cyclosporine**, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, estramustine, etoposide, etretinate, filgrastin, floxuridine, fludarabine, fluorouracil, florymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, limustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostin, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard,

vinblastine, vincristine and vindesine; immunological drugs such as vaccines and immune stimulants; insulin, calcitonin, parathyroid hormone and peptide and vasopressin hypothalamus releasing factor; beta adrenergic blockers such as timolol, levobunolol and betaxolol; cytokines, interleukines and growth factors epidermal growth factor, fibroblast growth factor, platelet derived growth factor, transforming growth factor beta, ciliary neurotrophic growth factor, glial derived neurotrophic factor, nerve growth factor (NGF), erythropoietin (EPO), placenta growth factor (PLGF), brain nerve growth factor (BNGF), vascular endothelial growth factor (VEGF) and monoclonal antibodies directed against such growth factors; anti-inflammatories such as hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone and triamcinolone; decongestants chosen from the group comprising phenylephrine, naphazoline and tetrahydrozoline; miotics and anti-cholinesterases chosen from the group comprising pilocarpine, carbachol, di-isopropyl fluorophosphate, phospholine iodine and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine; sympathomimetics such as epinephrine and vasoconstrictors and vasodilators; anticlotting agents such as heparin, antifibrinogen, fibrinolysin, anticlotting activase, antidiabetic agents such as acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin and aldose reductase inhibitors, hormones, peptides, nucleic acids, saccharides, lipids, glycolipids, glycoproteins and other macromolecules include endocrine hormones such as pituitary, insulin, insulin-related growth factor, thyroid, growth hormones; heat shock proteins; immunological response modifiers such as muramyl dipeptide, **cyclosporins**, interferons (including alpha-, beta- and gamma-interferons), interleukin-2, cytokines, FK506 (an epoxy-pyrido-oxaazacyclotricosine-tetrone, also known as Tacrolimus), tumor necrosis factor, pentostatin, thymopentin, transforming factor beta-.sub.2, erythropoietin; antineogenesis proteins (e.g. anti VEGF, Interferons); antibodies (monoclonal or polyclonal) or antibodies fragments, oligoaptamers, aptamers and gene fragments (oligonucleotides, plasmids, ribozymes, small interference RNA (SiRNA), nucleic acid fragments, peptides); immunomodulators such as endoxan, thalidomide, tamoxifene; antithrombolytic and vasodilator agents such as recombinant tissue plasminogen activator (rtPA), urokinase, plasmin, nitric oxide donors; nucleic acids optionally expressed to produce a protein that may have a variety of pharmacological, physiological or immunological activities.

L139 ANSWER 44 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2005-152322 [16] WPIX  
 CROSS REFERENCE: 2004-389738 [36]; 2005-151639 [16]; 2005-232906 [24];  
 2005-271944 [28]  
 DOC. NO. CPI: C2005-049322  
 TITLE: Non-translucent oil in water emulsion  
 , useful to treat e.g. dermatitis, bacterial infections  
 and dermatological disorders, comprises non-volatile  
 hydrophobic solvent, surface-active agent, gelling agent  
 and liquefied gas propellant.  
 DERWENT CLASS: A96 A97 B05 B07 C03 C07  
 INVENTOR(S): EINI, M; FRIEDMAN, D; TAMARKIN, D  
 PATENT ASSIGNEE(S): (FOAM-N) FOAMIX LTD  
 COUNTRY COUNT: 109  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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WO 2005011567 A2 20050210 (200516)\* EN 68 A61K000-00  
 RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE  
 LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE  
 DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG  
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ  
 OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG  
 US UZ VC VN YU ZA ZM ZW  
 AU 2004261063 A1 20050210 (200570) A61K007-00  
 EP 1670435 A2 20060621 (200643) EN A61K009-12  
 R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL  
 PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005011567	A2	WO 2004-IB2583	20040804
AU 2004261063	A1	AU 2004-261063	20040804
EP 1670435	A2	EP 2004-786401	20040804
		WO 2004-IB2583	20040804

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2004261063	A1 Based on	WO 2005011567
EP 1670435	A2 Based on	WO 2005011567

PRIORITY APPLN. INFO: US 2003-492385P 20030804  
 INT. PATENT CLASSIF.:  
 MAIN: A61K000-00; A61K007-00; A61K009-12

BASIC ABSTRACT:

WO2005011567 A UPAB: 20060906  
 NOVELTY - Non-translucent oil in water emulsion (A) (that is stable in its pre-dispensed state) for use as an alcohol-free foamable carrier, comprises:  
 (1) non-volatile hydrophobic solvent (a) (10-75 weight% of (A));  
 (2) surface-active agent (b) (0.1-5 weight%), having an HLB value of at least 9);  
 (3) gelling agent (c) (0.1-5 weight%) comprising an amphiphilic copolymer and;  
 (4) a liquefied gas propellant (d) (3-18 weight% of (A)).  
 ACTIVITY - Antibacterial; Fungicide; Virucide; Antiparasitic;  
 Antiinflammatory; Gastrointestinal-Gen.; Immunosuppressive; Antiallergic;  
 Endocrine-Gen.; Dermatological; Ophthalmological; Auditory; Gynecological;  
 Antiseborrheic; Cytostatic; Vulnerary; Anesthetic; Keratolytic.  
 MECHANISM OF ACTION - None given.  
 USE - (A) is useful in the treatment of diseases having an etiology of bacterial, fungal, viral, parasitic, inflammatory, autoimmune, allergic, hormonal and/or malignant. (A) is useful in the treatment of bio-abnormality, superficial condition or disorders of the skin, mucosal membrane, eye, ear, vagina or rectum. (A) is useful in the treatment of a disorder such as dermatosis, dermatitis, bacterial infections, fungal infections, parasitic infections, viral infections, disorders of hair follicles and sebaceous glands, acne, rosacea, scaling papular diseases, benign tumors, malignant tumors, reactions to sunlight, bullous diseases, pigmentation disorders, disorders of cornification, pressure sores, disorders of sweating, inflammatory reactions, xerosis, ichthyosis, allergy, burn, wound, cut and non-dermatological disorders that respond to transdermal delivery of the drug. (A) is useful to treat, alleviate or prevent dermatological disorder. (A) is

useful to prevent skin cancer or skin hyperpigmentation. (A) enhances hair growth and substantially limits or prevents hair growth. (A) is useful as local anesthetic agent or keratolytic agents. (All claimed.) No biological data given.

ADVANTAGE - (A) is stable in its pre-dispensed state and is a breakable therapeutic foam (claimed). (A) is alcohol free cosmetic or pharmaceutical foam. (A) is lightweight and thus economical. (A) contains a hydrophobic solvent, in any desirable concentration, which provides a refatting and skin soothing effect. (A) contains silicone oil in a therapeutically effective concentration and includes both water-soluble and oil-soluble active agents. (A) is easily spreadable, allowing treatment of large areas such as the arms, back, legs and the breast, and due to flow properties of (A) that spreads effectively into folds and wrinkles, by providing uniform distribution and absorption of the active agent without the need of extensive rubbing. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A12-V01; B01-B02; B01-C02; B01-C03; B03-F; B03-H;  
B04-A04; B04-A06; B04-A07C; B04-A08; B04-A10;  
B04-B01C; B04-B03D; B04-C02; B04-C03; B04-H05;  
B04-L03D; B05-A01A; B05-A01B; B05-B01M; B05-B01P;  
B05-C05; B05-C07; B06-H; B07-H; B09-D01; B10-A04;  
B10-A09A; B10-A10; B10-A17; B10-A22; B10-B01A;  
B10-B02; B10-B03B; B10-B04B; B10-C02; B10-C03;  
B10-C04; B10-D03; B10-E02; B10-E04; B10-H02;  
B10-J02; B14-A01; B14-A02; B14-A04; B14-B02;  
B14-C03; B14-C08; B14-G02A; B14-G02D; B14-H01;  
B14-H01W; B14-N02; B14-N03; B14-N07; B14-N14;  
B14-N17; B14-R01; B14-R02; C01-B02; C01-C02;  
C01-C03; C03-F; C03-H; C04-A04; C04-A06; C04-A07C;  
C04-A08; C04-A10; C04-B01C; C04-B03D; C04-C02;  
C04-C03; C04-H05; C04-L03D; C05-A01A; C05-A01B;  
C05-B01M; C05-B01P; C05-C05; C05-C07; C06-H; C07-H;  
C09-D01; C10-H02; C10-J02

TECH UPTX: 20050308

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (a) comprises 10-20 wt.% (preferably 20-75 wt.%) of (A).

(a) comprises a mixture of mineral oil and an emollient in a ratio of 2:8-8:2 on a weight basis.

(b) is a mixture of a non-ionic surfactant and an ionic surfactant in a ratio of 1:1-20:1 or 100:1-6:1.

(b) consists essentially of at least one non-ionic surfactant comprising a sucrose ester.

The amphiphilic copolymer is a cross linked copolymer of acrylic acid and a hydrophobic comonomer, amphiphilic starch derivatives, amphiphilic silicon polyols or copolyols, amphiphilic block polymers, pemulen polymeric surfactants, acrylates/10-30C alkyl acrylate crosspolymer, cetyl hydroxyethyl cellulose, acrylates /steareth-20 methacrylate copolymer, acrylates/ laureth-25 methacrylate copolymer, acrylates /beheneth-25 methacrylate copolymer, PRG-150/stearyl alcohol/SMDI copolymer, acrylates/vinyl isodecanoate, acrylates/steareth-20 itaconate copolymer, acrylates/ceteth-20 itaconate copolymer and acrylates/aminoacrylates/10-30C alkyl PEG 20 itaconate copolymer, amphiphilic silicone polymers, alkyl dimethicon copolyol, cetyl dimethicon copolyol, dimethicone copolyol PPG-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starches or amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol.

(b) further comprises a thickening agent of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum sodium alginate, xanthan gum, quince seed extract, tragacanth gum, starch, chemically modified starches, cellulose ethers, polyvinylpyrrolidone,

polyvinylalcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guar, carboxyvinyl polymers, polyvinyl alcohol polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers or polyvinylidene chloride polymers.

(A) further comprises a concentration of a drug.

(a) is a vegetable oil, a marine oil, a mineral oil, an emollient, a silicone oil and/or a plant-derived therapeutic oil at any proportion.

(b) and (c) comprises less than about 8% (preferably less than 5%) (w/w) of (A).

The active agent is a drug (cosmetically effective agent), insecticide, insect repellent, antiparasite (hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, malathion, piperonyl butoxide and/or any terpenol and derivatives), antiallergic agent (corticosteroids, non-steroidal antiinflammatory drugs, antihistamines, immunosuppressants and/or immunomodulating agent (preferably diphenhydramine, doxepin, phiramine maleate, chlorpheniramine and tripeleminamine, phenothiazines, promethazine hydrochloride, dimethindene maleate)), antiinflammatory agent (clobetasol propionate, halobetasol propionate, betamethasone dipropionate, betamethasone valerate, fluocinolone acetonide, halcinonide, betamethasone valerate, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide, hydrocortisone (preferably oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, salicylates, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioprofen, suprofen, alminoprofen, tiaprofenic, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone and trimethazone)), anticancer agent, retinoid (retinol, retinal, retinoic acid, etretinate, actiretin, isotretinoin, adapalene or tazarotene), an anti-wrinkle agent, sulfur-containing amino acids, thiol compounds, alpha hydroxy acids, lactic acid and lactic acid derivatives and salts, glycolic acid, glycolic acid derivatives and glycolic acid salts, beta-hydroxy acids, salicylic acid and salicylic acid salts and derivatives, phytic acid, lipoic acid, lysophosphatidic acid, skin peel agents, phenol, resorcinol, vitamin B3 compounds, niacinamide, nicotinic acid and nicotinic acid salts and esters, tocopheryl nicotinate, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide, retinoids, retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate and retinyl ascorbate, caffeine, theophylline, pentoxyphilline, dihydroxy acetone kojic acid, arbutin, nicotinic acid and nicotinic acid precursors, nicotinic acid salts, nicotinic acid derivatives, ascorbic acid, ascorbic acid salts or ascorbic acid derivatives, radical scavenger, herbal extract, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid and gallic acid alkyl esters, propyl gallate, uric acid, uric acid salts and alkyl esters, sorbic acid and sorbic acid salts, lipoic acid, N,N-diethylhydroxylamine, aminoguanidine, sulfhydryl compounds, glutathione, dihydroxy fumaric acid and fumaric acid salts, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin,

tea extract, grape skin/seed extract, melanin, rosemary extract, self-tanning agent, anti-acne active agent (further comprising retinoid, a keratolytically active agent and an anti-inflammatory agent), resorcinol, sulfur, salicylic acid, salicylate salts, benzoyl peroxide, retinoic acid, isotretinoin, adapalene, tazarotene, azelaic acid and azelaic acid derivatives, antibiotic agents, erythromycin and clyndamycin and zinc salts and complexes, skin whitening agents, exfoliant, epilating agent or depilating agent.

The active agent further comprises a screening agent which provides SFP value of at least about 30 (UVA absorber and a UVB absorber), decontaminating agent (oxidizing agent, iodine, iodine compounds, chlorohexidine, bleaching agent or surface-active agent).

The anti-inflammatory agent reduces the occurrence of pro-inflammatory cytokines or inhibits the effect of pro-inflammatory cytokines. The drug is an antibacterial drug (chloramphenicol, tetracyclines, synthetic and semi-synthetic penicillins, beta-lactams, quinolones, fluoroquinolones, macrolide antibiotics, peptide antibiotics, cyclosporines, metronidazole, free radical generating agents, iodine, chlorohexidine, benzoyl peroxide and/or hydrogen peroxide), an antifungal drug (azoles, diazoles, triazoles, miconazole, fluconazole, ketoconazole, clotrimazole, itraconazole griseofulvin, ciclopirox, amorolfine, terbinafine, amphotericin B, potassium iodide and/or flucytosine (5FC)) which is active against dermatophytes or candida, antiviral (vidarabine, acyclovir, gancyclovir, nucleoside-analog reverse transcriptase inhibitors, zidovudine, didanosine, zalcitabine, stavudine, lamivudine, nonnucleoside reverse transcriptase inhibitors, nevirapine, delavirdine, protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir, ribavirin, amantadine, rimantadine and interferon), photodynamic therapy agent, local anesthetic agent (benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine or phenol), nonsteroidal anti-inflammatory drug, retinoid, alpha hydroxy acid, beta hydroxy acid, keratolytic, antiproliferative, anticancer or antipigmentation drugs.

The active agent enhances hair growth and substantially limits or prevents hair growth.

L139 ANSWER 45 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN .  
 ACCESSION NUMBER: 2005-271944 [28] WPIX  
 CROSS REFERENCE: 2004-389738 [36]; 2005-151639 [16]; 2005-152322 [16];  
 2005-232906 [24]  
 DOC. NO. CPI: C2005-085070  
 TITLE: Alcohol-free foamable carrier, useful for treating e.g. dermatological disorder, comprises non-volatile hydrophobic solvent, surface-active agent, gelling agent comprising amphiphilic copolymer and liquefied gas propellant.  
 DERWENT CLASS: A96 B05 C03 D21  
 INVENTOR(S): EINI, M; FRIEDMAN, D; TAMARKIN, D  
 PATENT ASSIGNEE(S): (FOAM-N) FOAMIX LTD  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2005069566	A1	20050331	(200528)*		18	A61K007-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
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US 2005069566 A1 Provisional US 2003-492385P 20030804  
US 2004-911367 20040804

PRIORITY APPLN. INFO: US 2003-492385P 20030804; US  
2004-911367 20040804

INT. PATENT CLASSIF.:

MAIN: A61K007-00

BASIC ABSTRACT:

US2005069566 A UPAB: 20060906

NOVELTY - A non-translucent, oil in water emulsion comprises (weight%): liquid, non-volatile hydrophobic solvent (10 - 75, preferably 10 - 20 or 20 - 75); a surface-active agent (0.1 - 5) having an HLB of 9; a gelling agent (0.1 - 5) comprising an amphiphilic copolymer; and a liquefied gas propellant (3 - 18).

ACTIVITY - Dermatological; Cytostatic; Antiseborrheic; Anti-HIV; Virucide; Antibacterial; Fungicide; Antiparasitic; Antipsoriatic; Vulnerary; Keratolytic; Antiulcer.

MECHANISM OF ACTION - None given.

USE - As an alcohol-free foamable carrier useful for treating dermatological disorder and preventing skin cancer or skin hyperpigmentation (claimed). Also useful for treating contact dermatitis, seborrheic dermatitis, bacterial, fungal, parasitic and viral infections, psoriasis, Kaposi's sarcoma, sunburn, pemphigus, vitiligo, Melasma, Ichthyosis, actinic keratosis, ulcers and disorders of sweating.

ADVANTAGE - The composition is alcohol free; stable in pre-dispensed state; and is lightweight. The composition contains a hydrophobic solvent in any desirable concentration, that provides a refatting and skin soothing effect; and contains silicone oil in therapeutically effective concentrating and also both water-soluble and oil -soluble active agents. The foam composition is easily spreadable, allowing treatment of large areas e.g. arms, back, legs and breast. Due to flow properties of the foam, the foam spreads effectively into folds and wrinkles, thereby provides uniform distribution and absorption of the active agent without the need of extensive rubbing. The foam cleanses, beautifies, promotes or alters the appearance without affecting the body structure or function.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: A12-V04C; B01-B02; B01-B03; B02-E; B02-G; B03-A;  
B03-F; B03-H; B04-A06; B04-A07C; B04-A10; B04-B01C;  
B04-B03B; B04-B03D; B04-C02; B04-C03; B04-N02;  
B05-A01A; B05-B01P; B05-C06; B05-C08; B06-H; B07-H;  
B09-D01; B10-A04; B10-A10; B10-A17; B10-B01;  
B10-B02; B10-B03B; B10-C02; B10-C03; B10-C04;  
B10-D03; B10-E02; B14-A01; B14-A02; B14-A04;  
B14-B02; B14-C03; B14-C07; B14-G02; B14-H01;  
B14-N02; B14-N03; B14-N07; B14-N17; B14-R01;  
B14-R02; B14-S15; C01-B02; C01-B03; C02-E; C02-G;  
C03-A; C03-F; C03-H; C04-A06; C04-A07C; C04-A10;  
C04-B01C; C04-B03D; C04-C02; C04-C03; C04-N02;  
C05-A01A; C05-B01P; C05-C06; C05-C08; C06-H; C07-H;  
C09-D01; C10-A04; C10-A10; C10-A17; C10-B01;  
C10-B03B; C10-C02; C10-C03; C10-C04; C10-D03;  
C10-E02; C14-A01; C14-A02; C14-A04; C14-B02;  
C14-C03; C14-C07; C14-G02; C14-H01; C14-N02;  
C14-N03; C14-N07; C14-N17; C14-R01; C14-R02;  
C14-S15; D08-B09A

TECH UPTX: 20050504

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The



emulsion additionally comprises a thickening agent, therapeutically effective concentration of a drug that is cosmetically effective agent, a sunscreen agent (preferably UVA absorber or UVB absorber) providing SPF value of at least 30, a decontaminating agent and at least one agent selected from retinoid, keratolytically active agent and anti-inflammatory agent.

Preferred Components: The hydrophobic solvent comprises a mixture of mineral oil and an emollient in a weight ratio of 2:8 - 8:2. The surface-active agent is mixture of a non-ionic surfactant and an ionic surfactant in a ratio of 1:1 - 20:1 or 100:1 - 6:1 or at least one non-ionic surfactant. The hydrophobic solvent is selected from vegetable oil, marine oil, mineral oil, an emollient, silicone oil and/or plant-derived therapeutic oil. The non-ionic surfactant comprises a sucrose ester.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The amphiphilic copolymer is selected from cross linked copolymer of acrylic acid and hydrophobic comonomer, amphiphilic starch derivatives, amphiphilic silicon polyol or copolyol and amphiphilic block polymer (preferably Pemulen polymeric surfactant, acrylate/10-30C alkyl acrylate crosspolymer, cetyl hydroxyethyl cellulose, acrylate/steareth-20 methacrylate copolymer, acrylate/laureth-25 methacrylate copolymer, acrylate/beheneth-25 methacrylate copolymer, PRG-150/stearyl alcohol/4,4-methylene-bis-(cyclohexylisocyanate) (SMDI) copolymer, acrylate/vinyl isodecanoate, acrylate/steareth-20 itaconate copolymer, acrylate/ceteth-20 itaconate copolymer, acrylate/aminoacrylate/10-30C alkyl polyethylene glycol-20 itaconate copolymer, amphiphilic silicone polymer, alkyl dimethicon copolyol, cetyl dimethicon copolyol, dimethicone copolyol polypropylene-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starch, and amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol). The thickening agent is locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenan gum sodium alginate, xanthan gum, quince seed extract, tragacanth gum, starch, chemically modified starch, cellulose ether, polyvinylpyrrolidone, polyvinyl alcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic cellulose, cationic guar, carboxyvinyl polymer, polyvinyl alcohol polyacrylic acid polymer, polymethacrylic acid polymer, polyvinyl acetate polymer, polyvinyl chloride polymer or polyvinylidene chloride polymer.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The drug is selected from those for the treatment of bio-abnormality, superficial condition, disorder of the skin, mucosal membrane, eye, ear, vagina or rectum, disease having etiology selected from bacterial, fungal, viral, parasitic, inflammatory, autoimmune, allergic, hormonal and/or malignant, or disorders e.g. dermatosis, dermatitis, bacterial, fungal, parasitic and viral infections, acne, rosacea, scaling popular diseases, benign tumor, malignant tumor, reactions of sunlight, bullous disease, pigmentation disorder, pressure sore, disorders of hair follicles and sebaceous glands, disorders of cornification and sweating, inflammatory reactions, xerosis, ichthyosis, allergy, burn, wound, cut and non-dermatological disorders responding to transdermal delivery of the drug. The drug is an antibacterial material, antifungal material, antiviral, insecticide and insect repellent, anti-allergic agent, anti-inflammatory agent, anticancer agent, photodynamic therapy agent, local anesthetic agent, retinoid, anti-wrinkle agent, radical scavenger, herbal extract, self-tannin agent, anti-acne active agent, skin whitening agent, hair growth enhancer, an exfoliant, an epilating agent or depilating agent.

The antibacterial material is chloramphenicol, tetracycline, synthetic and semi-synthetic penicillin, beta-lactam, quinolone, fluoroquinolone, macrolide antibiotic, peptide antibiotic, cyclosporines,

metronidazole, free radical generating agent, iodine, chlorohexidine, benzoyl peroxide and/or hydrogen peroxide.

The antifungal drug is active against dermatophytes or Candida and selected from azoles, diazoles, triazoles, miconazole, fluconazole, ketoconazole, clotrimazole, itraconazole, griseofulvin, ciclopirox, amorolfine, terbinafine, amphotericin B, potassium iodide and/or flucytosine (5FC).

The antiviral drug is vidarabine, acyclovir, gancyclovir, nucleoside-analog reverse transcriptase inhibitors, AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), 3TC (lamivudine), non-nucleoside reverse transcriptase inhibitors, nevirapine, delavirdine, protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir, ribavirin, amantadine, rimantadine or interferon.

The antiparasite is selected from hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, malathion, piperonyl butoxide, any terpenol and/or their derivatives.

The antiallergic agent is corticosteroid, non-steroidal antiinflammatory drug, antihistamine, immunosuppressant and/or immunomodulating agent. The antiallergic agent is doxepin, diphenhydramine, phirilamine maleate, chlorpheniramine, tripeleennamine, phenothiazines, promethazine hydrochloride and/or dimethindene maleate.

The anti-inflammatory agent is corticosteroid, non-steroidal antiinflammatory drug, immunosuppressant and/or immunomodulator (preferably clobetasol proprionate, halobetasol proprionate, betamethasone dipropionate, betamethasone valerate, fluocinolone acetonide, halcinonide, betamethasone valerate, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide and/or hydrocortisone or oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, salicylate, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone or trimethazone).

The anesthetic is selected from benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, ketamine, pramoxine and phenol. The retinoid is retinol, retinal, retinoic acid, tretinate, tretin, isotretinoin, adapalene or tazarotene.

The active agent is selected from sulfur-containing amino acid, thiol compound, alpha hydroxy acid, lactic acid and lactic acid derivatives and salts, glycolic acid, glycolic acid derivatives and glycolic acid salts, beta-hydroxy acid, salicylic acid and salicylic acid salts and derivatives, phytic acid, lipoic acid, lysophosphatidic acid, skin peel agent, phenol, resorcinol, vitamin B3 compounds, niacinamide, nicotinic acid and nicotinic acid salts and esters, tocopheryl nicotinate, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide, niacinamide N-oxide, retinoid, retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, retinyl ascorbate, caffeine, theophylline, pentoxyphylline, dihydroxy acetone kojic acid, arbutin, nicotinic acid or its precursors, salts or derivatives, ascorbic acid or its salts or derivatives, ascorbyl ester of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids or their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid or its

alkyl esters, propyl gallate, uric acid or its salts or alkyl esters, sorbic acid or its salts, lipoic acid, N,N-diethylhydroxylamine, aminoguanidine, sulfhydryl compounds, glutathione, dihydroxy fumaric acid or its salts, lyncine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extract, grape skin/seed extract, melanin, rosemary extract, sulfur, salicylic acid, salicylate salts, benzoyl peroxide, retinoic acid, isotretinoin, adapalene, tazarotene, azelaic acid or its derivatives, antibiotic agent, erythromycin, clyndamycin and zinc salts or complexes.

The anti-inflammatory agent or anti-allergic agent reduces the occurrence of pro-inflammatory cytokines or inhibits the effect of proinflammatory cytokines.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The decontaminating agent is selected from an oxidizing agent, iodine, iodine compound, chlorohexidine, bleaching agent and surface-active agent.

L139 ANSWER 46 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2004-689154 [67] WPIX  
 CROSS REFERENCE: 2004-717813 [70]; 2005-699632 [72]  
 DOC. NO. CPI: C2004-244217  
 TITLE: Self-emulsifying composition useful with therapeutic drug used in making therapeutic composition, e.g. ophthalmic composition, comprises oil globules containing surfactant and polar oil components.  
 DERWENT CLASS: B05  
 INVENTOR(S): HUTH, S; YU, Z; COOK, J N; CRAWFORD, L L; HUTH, S W  
 PATENT ASSIGNEE(S): (HUTH-I) HUTH S; (YUZZ-I) YU Z; (ADME-N) ADVANCED MEDICAL OPTICS INC  
 COUNTRY COUNT: 109  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2004185068	A1	20040923	(200467)*		26	A61K007-00	
WO 2004082625	A2	20040930	(200467)	EN		A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							
EP 1603607	A2	20051214	(200582)	EN		A61M001-00	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR							
AU 2004222295	A1	20040930	(200612)			A61K009-107	
BR 2004008516	A	20060307	(200619)			A61K009-107	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004185068	A1	US 2003-392375	20030318
WO 2004082625	A2	WO 2004-US8076	20040317
EP 1603607	A2	EP 2004-757532	20040317
		WO 2004-US8076	20040317
AU 2004222295	A1	AU 2004-222295	20040317
BR 2004008516	A	BR 2004-8516	20040317

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1603607	A2 Based on	WO 2004082625
AU 2004222295	A1 Based on	WO 2004082625
BR 2004008516	A Based on	WO 2004082625

PRIORITY APPLN. INFO: US 2003-392375 20030318

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K007-00; A61K009-107; A61M001-00

## BASIC ABSTRACT:

US2004185068 A UPAB: 20060320

NOVELTY - A self-emulsifying composition comprises oil globules containing surfactant and polar oil components. The oil globules have average size of less than 1 micro m dispersed in aqueous phase. The surfactant component comprises one or two surfactants. The polar oil and surfactant components are selected to self-emulsify when mixed without mechanical homogenization.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for preparing self-emulsifying composition comprising preparing oil phase comprising polar oil and surfactant components, preparing aqueous phase at temperature that permits self-emulsification, and mixing oil phase and aqueous phase to form emulsion without mechanical homogenization.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - Useful with therapeutic drug used in making therapeutic composition, e.g. ophthalmic composition (claimed).

ADVANTAGE - The invention is prepared without mechanical homogenization. It provides low weight ratio of emulsifying component to oil component and fewer chemical toxicity concerns, resulting in comfort and safety advantages over emulsions using at least two emulsifiers.

DESCRIPTION OF DRAWING(S) - The figure shows a flow chart of the preparation of ophthalmic self-emulsifying compositions. Dwg:1/5

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B02-C01; B03-L; B04-B01C1; B04-C03B; B04-H03;  
B06-D06; B10-C04E

TECH UPTX: 20041019

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The surfactant component has hydrophobic portion containing two parts. The first part is oriented proximal to the aqueous phase. The first part is larger than the second part of the hydrophobic portion of the surfactant component. The second part is oriented towards the interior of the oil globules. The first hydrophobic portion has longer chain length than the second hydrophobic portion. The composition also comprises additional surfactant that does not interfere with self-emulsification. The oil component comprises castor oil or natural oil. The surfactant component is a compound with ether(s) formed from ethylene oxide units (1-100) and carbon atom(s), compound with ether(s) formed from ethylene oxide units (1-100) and 12-22C fatty acid(s), and/or compound with ether, ester, and/or amide formed from ethylene oxide units (1-100) and vitamin and/or its derivative. The surfactant component containing one surfactant is Lumulse GHR-40, or TGPS. The oil globules has average size of less than 0.25, preferably less than 0.15microm. The ophthalmic composition contains self-emulsifying composition and drug that is therapeutic when administered to the eye. The therapeutic compound is cyclosporin, prostaglandins, or Brimonidine (salt). The polar

oil is castor or natural oil.

L139 ANSWER 47 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2004-071249 [07] WPIX  
DOC. NO. NON-CPI: N2004-057331.  
DOC. NO. CPI: C2004-029443  
TITLE: Drug delivery system for delivery of drug into  
eye comprises a contact lens having ophthalmic  
drug in form of nanoparticles nanoencapsulated in a  
material.  
DERWENT CLASS: A14 A28 A96 B05 B07 D22 P32  
INVENTOR(S): CHAUHAN, A; GULSEN, D  
PATENT ASSIGNEE(S): (CHAU-I) CHAUHAN A; (GULS-I) GULSEN D; (UYFL) UNIV  
FLORIDA  
COUNTRY COUNT: 103  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003103549	A1	20031218	(200407)*	EN	46	A61F013-00	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							
US 2004096477	A1	20040520	(200434)			A61K009-00	
AU 2003248624	A1	20031222	(200445)			A61F013-00	
US 2004241207	A1	20041202	(200481)			A61K009-00	
BR 2003011585	A	20050510	(200533)			A61F013-00	
EP 1534202	A1	20050601	(200536)	EN		A61F013-00	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR							
JP 2005528185	W	20050922	(200563)		23	A61L027-00	
CN 1674841	A	20050928	(200610)			A61F013-00	
KR 2005037992	A	20050425	(200637)			A61F009-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003103549	A1	WO 2003-US17736	20030605
US 2004096477	A1 Provisional	US 2002-385571P	20020605
		US 2003-454836	20030605
AU 2003248624	A1	AU 2003-248624	20030605
US 2004241207	A1 Provisional	US 2002-385571P	20020605
	CIP of	US 2003-454836	20030605
		US 2004-802058	20040317
BR 2003011585	A	BR 2003-11585	20030605
		WO 2003-US17736	20030605
EP 1534202	A1	EP 2003-757353	20030605
		WO 2003-US17736	20030605
JP 2005528185	W	WO 2003-US17736	20030605
		JP 2004-510672	20030605
CN 1674841	A	CN 2003-818898	20030605
KR 2005037992	A	WO 2003-US17736	20030605
		KR 2004-719648	20041203

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003248624	A1 Based on	WO 2003103549
BR 2003011585	A Based on	WO 2003103549
EP 1534202	A1 Based on	WO 2003103549
JP 2005528185	W Based on	WO 2003103549
KR 2005037992	A Based on	WO 2003103549

PRIORITY APPLN. INFO: US 2002-385571P 20020605; US  
2003-454836 20030605; US  
2004-802058 20040317

INT. PATENT CLASSIF.:

MAIN: A61F009-00; A61F013-00; A61K009-00; A61L027-00  
SECONDARY: A61F002-00; A61K009-24; G02C013-00

BASIC ABSTRACT:

WO2003103549 A UPAB: 20040128

NOVELTY - A drug delivery system (S) comprises a contact lens having an ophthalmic drug in form of nanoparticles (particle size less than 50 nm) nanoencapsulated in a material. The ophthalmic drug diffuses into and migrates through contact lens and into post-lens tear film when contact lens is placed in eye.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a kit containing a first components which comprises (S), and a second components which comprises at least one storage container for the first component, where the storage container additionally comprises a material which prevents the diffusion and migration of the drug during storage;

(2) preparation of (S) involving preparing the contact lens from material which incorporates the nanoencapsulated ophthalmic drug such that the nanoencapsulated drug is uniformly dispersed throughout the contact lens; and

(3) an article of manufacture comprising a packaging material and (S) or the kit.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - For directly delivery of drug into eye (claimed).

ADVANTAGE - The drug has particle size of 50 nm. (S) reduces drug loss, eliminates systemic side effects, improves drug efficacy and ameliorates symptoms associated with pathologic conditions of the eye.

Dwg.0/21

FILE SEGMENT: CPI GMPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: A12-V01; A12-V02A; B02-C01; B04-B04D2; B04-B04E;  
B04-C02C; B04-C02D; B04-C02E; B04-C03; B06-A03;  
B06-D02; B06-D04; B07-A02A; B07-A02B; B07-D09;  
B07-D12; B07-E03; B07-F03; B10-B02A; B10-B02F;  
B12-M11E; B14-N03; D09-C01A

TECH UPTX: 20040128

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The nanoparticles (1 - 5 wt.%) are dispersed within the contact lens such that the lens is optically transparent. The contact lens is a soft contact lens. The ophthalmic drug is selected from lidocaine, timolol, ciproflaxin, cyclosporin A, pilocarpine, antiparasitic or anti-protozoal drugs (e.g. ivermectin, pyrimethamine), non-steroids (e.g. acular and voltaren), steroids (e.g. prednisilone acetate), antibiotics (e.g. ciloxan), gentamycin and/or cephalosporins. The ophthalmic drug is nanoencapsulated in an oil-in-water emulsion. The encapsulation material is microemulsion nanodroplets, tocopherol derivatives stabilized nano-sized emulsion particles, gelatin, agarose hydrogel, PMMA, carboxymethyl dextran magnetic nanoparticles and/or biotinylated pullulan acetate. The material is saturated aqueous

solution of ophthalmic drug.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The contact lens comprises poly-2-hydroxyethylmethacrylate. The encapsulation material is biodegradable poly(alkylcyanoacrylates), polybutylcyanoacrylate, polyhexylcyanoacrylate, polyethylcyanoacrylate, (polyisobutylcyanoacrylate), polycyanoacrylate, silica nanospheres, PEG'ylated core-shell nanoparticles, biodegradable PLGA (poly(D,L-lactide-co-glycolide)) particles, (poly lactic acid), PGA, PLG (poly(D,L-glycolide))polymeric nanoparticles, low pH sensitive PEG stabilized plasmid-lipid nanoparticles, polysaccharides grafted with polyesters (amphiphilic copolymers), PLA-PEG nanoparticles, nanoparticles composed of hydrophilic proteins coupled with apolipoprotein E, biodegradable poly(vepsiln-caprolactone)nanoparticles, poly(methylidene malonate), poly(E-caprolactone), sodium alginate, biotinylated poly(ethylene glycol) conjugated with lactobionic acid, poly(vinyl alcohol)hydrogel, and/or diblock copolymers.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The encapsulation material is chitosan nanoparticles, human serum albumin nanoparticles, liposomes, biocompatible gliadin nanoparticles and/or nanoparticles composed of hydrophilic proteins coupled with apolipoprotein E.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The encapsulation material is silica nanospheres, and/or biodegradable calcium phosphate legumin.

L139 ANSWER 48 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2004-031226 [03] WPIX  
DOC. NO. CPI: C2004-010317  
TITLE: **Emulsion** for forming tear film on **eye** surface, for preventing dry **eye**, comprises mixture containing non-polar phospholipid, non-polar oil, non-toxic **emulsifying** agent and cationic lipid dispersed in water.  
DERWENT CLASS: A96 B04 B05  
INVENTOR(S): BENITA, S; LAMBERT, G  
PATENT ASSIGNEE(S): (NOVA-N) NOVAGALI SAS; (YISS) YISSUM RES DEV CO HEBREW UNIV JERUSALEM; (NOVA-N) NOVAGALI PHARMA SA; (YISS) YISSUM RES & DEV CO  
COUNTRY COUNT: 99  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2003108626	A1	20030612	(200403)*		5	A61K035-78	
WO 2003053405	A1	20030703	(200403)#	EN		A61K009-107	
	RW:	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
		NL OA PT SD SE SL SZ TR TZ UG ZW					
	W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
		DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR					
		KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT					
		RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
US 6656460	B2	20031202	(200404)			A61K031-74	
AU 2002214233	A1	20030709	(200428)#			A61K009-107	
EP 1441696	A1	20040804	(200452)#	EN		A61K009-107	
	R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
		RO SE SI TR					
CN 1558751	A	20041229	(200524)#			A61K009-107	
JP 2005513097	W	20050512	(200532)		20	A61K009-107	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003108626	A1	US 2001-985185	20011101
WO 2003053405	A1	WO 2001-IL1015	20011101
US 6656460	B2	US 2001-985185	20011101
AU 2002214233	A1	WO 2001-IL1015	20011101
		AU 2002-214233	20011101
EP 1441696	A1	EP 2001-982692	20011101
		WO 2001-IL1015	20011101
CN 1558751	A	CN 2001-823757	20011101
		WO 2001-IL1015	20011101
JP 2005513097	W	WO 2001-IL1015	20011101
		JP 2003-554164	20011101

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002214233	A1 Based on	WO 2003053405
EP 1441696	A1 Based on	WO 2003053405
JP 2005513097	W Based on	WO 2003053405

PRIORITY APPLN. INFO: US 2001-985185 20011101; WO  
2001-IL1015 20011101; AU  
2002-214233 20011101; EP  
2001-982692 20011101; CN  
2001-823757 20011101; JP  
2003-554164 20011101

## INT. PATENT CLASSIF.:

MAIN: A61K009-107; A61K031-74; A61K035-78  
SECONDARY: A61K031-355; A61K031-436; A61K031-4366; A61K031-685;  
A61K031-706; A61K038-00; A61K038-13; A61K038-133;  
A61K047-10; A61K047-18; A61K047-24; A61K047-44;  
A61P027-02; A61P027-022; A61P027-04

## BASIC ABSTRACT:

US2003108626 A UPAB: 20040112

NOVELTY - An emulsion comprises a mixture containing non-polar phospholipid, non-polar oil, non-toxic emulsifying agent and cationic lipid dispersed in water. The emulsion imparts a net positive charge to the tear film, hence gets electrostatically attracted to the anionic eye surface and inhibits evaporation of fluids from the eye surface. The emulsion is applied to the anionic surface of eyes.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for treatment of dry eye, which involves preparing the above emulsion by dispersing the mixture in water; and applying the obtained emulsion to the eye surfaces to form a tear film, which is electrostatically attracted/adhered to the anionic surface of eyes.

ACTIVITY - Ophthalmological.

No test details are given.

MECHANISM OF ACTION - None given.

USE - For treating dry eye (claimed).

ADVANTAGE - The emulsion composition effectively treats dry eye condition, when applied topically on the eye surface. The emulsion forms tear film that lubricate the eyes and inhibit fluid loss from the eye surface. The film formed on the eye surface is not washed away easily, hence the effect is maintained for prolonged period. The tear film coating the eye surface does



not produce adverse effects. The ingredients in the mixture improves the emulsion stability. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A12-V04C; B02-C01; B02-S; B02-T; B04-B01B; B04-C03C;  
B05-B01P; B06-A01; B10-A22; B10-B04B; B10-E04C;  
B12-M03; B14-N03

TECH UPTX: 20040112

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The mixture comprises castor oil, 0.1-0.5% of Lipoid E-80 (phospholipid), cationic lipid such as stearylamine or oleylamine, 0.5-2.0% of poloxamer as emulsifying agent. The mixture further comprises vitamin E, glycerol, cationic preservative/antiseptic agent e.g. benzalkonium chloride and water-insoluble medicaments such as cyclosporin, tacrolimus or sirolimus. The size of the ingredients are made into submicron droplets by formulating as an emulsion.

L139 ANSWER 49 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2003-186117 [19] WPIX  
DOC. NO. CPI: C2003-049221  
TITLE: Stable, well tolerated gel-emulsion for use in the eye, containing mixture of polyacrylate with polyvinyl alcohol, polyvinyl pyrrolidone, dextran or cellulose derivative and optionally ophthalmological drug.  
DERWENT CLASS: A11 A14 A96 B04 B07  
INVENTOR(S): KREITMEIER, P; MUGGENTHALER, M; POLZER, H; POLZER,  
PATENT ASSIGNEE(S): (MEDP-N) MEDPROJECT PHARMA-ENTWICKLUNGS  
COUNTRY COUNT: 26  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
EP 1275376	A2	20030115	(200319)*	GE	12	A61K009-10	
	R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
		RO SE SI TR					
DE 10132876	A1	20030130	(200319)			C08L033-08	
EP 1275376	B1	20060419	(200630)	GE		A61K009-10	
	R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
		RO SE SI TR					
DE 50109549	G	20060524	(200635)			A61K009-10	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1275376	A2	EP 2001-124148	20011010
DE 10132876	A1	DE 2001-10132876	20010706
EP 1275376	B1	EP 2001-124148	20011010
DE 50109549	G	DE 2001-00109549	20011010
		EP 2001-124148	20011010

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 50109549	G Based on	EP 1275376

PRIORITY APPLN. INFO: DE 2001-10132876 20010706  
INT. PATENT CLASSIF.:

MAIN: A61K009-10; C08L033-08  
SECONDARY: A61K009-00; A61K009-107; A61K031-375; A61K031-566;  
A61K038-13; A61K047-00; A61K047-32; A61K047-34;  
A61K047-38; C08J003-075; C08L005-02; C08L029-04;  
C08L039-06

BASIC ABSTRACT:

EP 1275376 A UPAB: 20030320

NOVELTY - A droppable gel-emulsion (A), especially for use in the eye, contains a polymer mixture of polyacrylate (I) with polyvinyl alcohol, polyvinyl pyrrolidone, dextran or a cellulose derivative (II).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of (A).

ACTIVITY - Ophthalmological. No biological test data provided.

MECHANISM OF ACTION - None Given. No biological test data provided.

USE - The use (I) is claimed in the production of a medicament for use in the eye, where (A) optionally contains at least one ophthalmological drug, specifically estradiol or cyclosporin A.

ADVANTAGE - (I) has a suitable starting viscosity (1000-50000 mPa.s) to be droppable from a conventional eye-drop bottle; has an adjustable residual viscosity in the eye, to provide tolerance and the required residence time; and can incorporate all types of water- or oil-soluble active agents and preservatives conventionally used in ophthalmology. The gel-forming combination of polymers (I) and (II) is effective in relatively small amounts, and provides stable, sterilizable, well tolerated gels.

Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A04-F06E5; A12-V01; B01-A02; B02-C01; B04-C02A;  
B04-C02C; B04-C03B; B10-A07; B10-A22; B10-B01B;  
B10-E04C; B12-M03; B14-N03

TECH UPTX: 20030320

TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The polyacrylate (I) has a molecular weight of 1000000-4000000. (I) additionally contains salts (specifically sodium acetate) to adjust the initial viscosity. (II) is preferably polyvinyl pyrrolidone, in which case (I) specifically contains 0.05-3 (especially 0.05-1)% (I) and 0.05-10 (especially 1-7)% (II). Alternatively (II) is hydroxypropyl methyl cellulose, polyvinyl alcohol or dextran. (I) optionally contains glycerol, sorbitol or mannitol as additive, a preservative (specifically benzalkonium chloride) and/or a base (specifically trometamol or lysine). Preparation: Claimed preparation of (I) involves:

(i) preparing an aqueous dispersion of the polyacrylate (I), containing an isotonic agent and optionally preservatives, then forming a gel (optionally with addition of base and salts);  
(ii) finely dispersing the oil phase (optionally containing ophthalmological drug(s)) in an aqueous solution of the polymer (II) (optionally containing at least part of the preservative), using a homogenizer; and  
(iii) homogeneous incorporating the mixture from (ii) in the gel from (i) under stirring.

L139 ANSWER 50 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2003-523923 [50] WPIX  
DOC. NO. CPI: C2003-141115  
TITLE: An emulsion for topical application to the eye for the treatment of dry eye comprises water, a non-polar phospholipid, a non-polar oil, an emulsifying agent and a cationic lipid..  
DERWENT CLASS: A96 B02 B04 B07 D22

INVENTOR(S): BENITA, S; LAMBERT, G  
 PATENT ASSIGNEE(S): (NOVA-N) NOVAGALI SAS; (YISS) YISSUM RES DEV CO HEBREW  
 UNIV JERUSALEM; (NOVA-N) NOVAGALI PHARMA SA  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
AU 2001087320	A	20030508	(200350)*		17	A61P027-04	
AU 782913	B2	20050908	(200568)			A61P027-04	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
AU 2001087320	A	AU 2001-87320	20011102
AU 782913	B2	AU 2001-87320	20011102

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 782913	B2 Previous Publ.	AU 2001087320

PRIORITY APPLN. INFO: AU 2001-87320 20011102

INT. PATENT CLASSIF.:

MAIN: A61P027-04  
 SECONDARY: A61K009-107

BASIC ABSTRACT:

AU 200187320 A UPAB: 20030805

NOVELTY - An emulsion for topical application to the eye comprises water and a mixture including a non-polar phospholipid, a non-polar oil, a non-toxic emulsifying agent and a cationic lipid.

DETAILED DESCRIPTION - An emulsion for topical application to the eye to form a tear film which lubricates the eye and inhibits the evaporation of fluid therefrom which comprises water and a mixture dispersed in the water including a non-polar phospholipid, a non-polar oil, a non-toxic emulsifying agent and a cationic lipid which imparts a net positive charge to the tear film, causing it to be electrostatically attracted to the anionic eye surface and to adhere there and so inhibit evaporation.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - The composition is used for the treatment of dry eye forming an artificial tear film on the surface of the eye, providing lubrication and preventing evaporation therefrom, it may also be used to treat eye disease.

ADVANTAGE - The composition has a net positive charge and so causes the film to adhere electrostatically to the entire anionically charged eye surface, giving even distribution. Dwg.0/0

FILE SEGMENT:

CPI

FIELD AVAILABILITY:

AB; DCN

MANUAL CODES:

CPI: A12-V01; B02-C; B02-S; B03-H; B04-B01B; B04-B01C;  
 B05-B01P; B06-E05; B10-A22; B10-E04C; B12-M02B;  
 B14-N03; D09-A01C

TECH

UPTX: 20030805

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The oil is castor oil, the phospholipid is Lipoid E-80, the cationic lipid is stearylamine or oleylamine and the emulsifying agent is poloxamer. The composition may further comprise one or more of the following: vitamin E, glycerol, a cationic antiseptic agent such as benzalkonium chloride, a water-insoluble medicament to treat eye

disease e.g. cyclosporin, tacrolimus or sirolimus. The relative percentage of the phospholipid in the emulsion is in the range 0.1-2 %, the castor oil 0.5-10 %, the cationic lipid 0.1-0.5 % and the emulsifying agent 0.5-2 %.

L139 ANSWER 51 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2002-139762 [18] WPIX  
 CROSS REFERENCE: 2002-139764 [12]  
 DOC. NO. CPI: C2002-043031  
 TITLE: Stable, well tolerated composition for topical drug administration to the eye, comprises solution of water-insoluble drug in a neutral oil, preferably medium chain triglyceride.  
 DERWENT CLASS: B05 B07  
 INVENTOR(S): KLOECKER, N  
 PATENT ASSIGNEE(S): (AUDI-N) AUDIT INST MEDICAL SERVICES & QUALITY AS  
 COUNTRY COUNT: 96  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2001097774	A2	20011227	(200218)*	GE	12	A61K009-00	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW							
DE 10030378	A1	20020314	(200226)			A61K047-44	
AU 2001083876	A	20020102	(200230)			A61K009-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001097774	A2	WO 2001-EP7036	20010621
DE 10030378	A1	DE 2000-10030378	20000621
AU 2001083876	A	AU 2001-83876	20010621

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001083876	A Based on	WO 2001097774

PRIORITY APPLN. INFO: DE 2000-10030378 20000621  
 INT. PATENT CLASSIF.:

MAIN: A61K009-00; A61K047-44  
 SECONDARY: A61K031-565

BASIC ABSTRACT:

WO 200197774 A UPAB: 20020513  
 NOVELTY - A composition (A) for topical application to the eye comprises one water-insoluble or sparingly water-soluble active agent (I) dissolved in a neutral oil (II).  
 ACTIVITY - Ophthalmological.  
 No biological data given.  
 MECHANISM OF ACTION - None given.  
 USE - For topical administration of drugs to the eye.  
 ADVANTAGE - (A) is well tolerated by the eye; adheres well to the eye surface to provide good resorption via the cornea or ocular mucosa; is stable;

can be sterile filtered; requires no addition of (potentially allergenic) preservatives or emulsifiers; is easily administered in exact doses; and can be prepared rapidly and inexpensively.

Dwg.0/0

FILE SEGMENT: CPI  
 FIELD AVAILABILITY: AB; DCN  
 MANUAL CODES: CPI: B01-A02; B01-B02; B01-C05; B03-F; B03-H; B04-A01;  
 B04-B01B; B04-B01C; B04-C01C; B04-N01A; B05-B01P;  
 B06-A02; B06-D04; B06-D09; B07-B03; B07-D09;  
 B10-A06; B10-B01B; B10-B02A; B10-B02E; B10-B03A;  
 B10-C03; B10-E04; B10-J01; B12-M05; B12-M06;  
 B14-N03; B14-S08

L139 ANSWER 52 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-035685 [05] WPIX

DOC. NO. CPI: C2002-010255

TITLE: Cyclosporin-containing topical ophthalmological formulations, e.g. for treating dry eye kerato-conjunctivitis or Sjogren syndrome, contain hyaluronic acid and polysorbate 80 to improve bioavailability and tolerance.

DERWENT CLASS: A96 B03 B04

INVENTOR(S): DI NAPOLI, G; DIENABORY, G; NAPOLI, G D

PATENT ASSIGNEE(S): (MEDI-N) LAB MEDIDOM SA; (MEDI-N) LAB MEDIDOM CO LTD;  
 (NAPO-I) NAPOLI G D

COUNTRY COUNT: 35

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
EP 1142566	A1	20011010	(200205)*	FR	15	A61K009-08	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR							
AU 2001033404	A	20011011	(200205)			A61P027-04	
BR 2001001332	A	20011106	(200205)			A61K038-13	
CA 2342133	A1	20011007	(200205)	EN		A61K038-13	
CZ 2001001229	A3	20011114	(200205)			A61K009-08	
SK 2001000460	A3	20011106	(200205)			A61K009-08	
US 2001041671	A1	20011115	(200205)			A61K038-13	
JP 2001316284	A	20011113	(200207)		10	A61K038-00	
ZA 2001002769	A	20011224	(200212)		27	A61K000-00	
CN 1317342	A	20011017	(200213)			A61K038-13	
EP 1142566	B1	20031001	(200365)	FR		A61K009-08	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU MC NL PT RO SE SI TR							
DE 60100866	E	20031106	(200381)			A61K009-08	
US 6677304	B2	20040113	(200405)			A61K038-00	
ES 2206363	T3	20040516	(200434)			A61K009-08	
US 2004106546	A1	20040603	(200436)			A61K038-13	
CZ 294385	B6	20041215	(200501)			A61K009-08	
AU 778858	B2	20041223	(200510)			A61K038-18	
US 6953776	B2	20051011	(200567)			A61K038-13	
CN 1185009	C	20050119	(200620)			A61K038-13	
SK 285220	B6	20060907	(200662)			A61K009-08	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1142566	A1	EP 2001-107223	20010323

AU 2001033404	A	AU 2001-33404	20010404
BR 2001001332	A	BR 2001-1332	20010406
CA 2342133	A1	CA 2001-2342133	20010327
CZ 2001001229	A3	CZ 2001-1229	20010404
SK 2001000460	A3	SK 2001-460	20010405
US 2001041671	A1	US 2001-818213	20010327
JP 2001316284	A	JP 2001-109077	20010406
ZA 2001002769	A	ZA 2001-2769	20010404
CN 1317342	A	CN 2001-112484	20010406
EP 1142566	B1	EP 2001-107223	20010323
DE 60100866	E	DE 2001-00100866	20010323
		EP 2001-107223	20010323
US 6677304	B2	US 2001-818213	20010327
ES 2206363	T3	EP 2001-107223	20010323
US 2004106546	A1 Div ex	US 2001-818213	20010327
		US 2003-721007	20031121
CZ 294385	B6	CZ 2001-1229	20010404
AU 778858	B2	AU 2001-33404	20010404
US 6953776	B2 Div ex	US 2001-818213	20010327
		US 2003-721007	20031121
CN 1185009	C	CN 2001-112484	20010406
SK 285220	B6	SK 2001-460	20010405

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 60100866	E Based on	EP 1142566
ES 2206363	T3 Based on	EP 1142566
US 2004106546	A1 Div ex	US 6677304
CZ 294385	B6 Previous Publ.	CZ 2001001229
AU 778858	B2 Previous Publ.	AU 2001033404
US 6953776	B2 Div ex	US 6677304
SK 285220	B6 Previous Publ.	SK 2001000460

PRIORITY APPLN. INFO: CH 2000-694 20000407

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K009-08; A61K038-00; A61K038-13;  
A61K038-18; A61P027-04

SECONDARY: A61K031-715; A61K031-728; A61K038-12; A61K047-26;  
A61K047-34; A61K047-36; A61P027-00; A61P027-02;  
A61P029-00; A61P037-06

BASIC ABSTRACT:

EP 1142566 A UPAB: 20020123

NOVELTY - Topical ophthalmological formulations (I) comprise aqueous solutions containing a **cyclosporin** (a), hyaluronic acid or its salt (b) and polysorbate 80 (c).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (a) in combination with (b) and (c) for the preparation of f(I).

ACTIVITY - Ophthalmological; immunosuppressive; antiinflammatory.

A composition contained (by weight): **cyclosporin** A (0.20 %), sodium hyaluronate (0.10 %), Tween 80 (RTM; polysorbate 80) (5.00 %), disodium hydrogen phosphate dodecahydrate (0.08%), sorbitol (5.16%) and purified water. The pH was 7.0-7.4 and the osmolality was 295-305. The composition showed good ocular tolerance in the Draize test and formed no precipitate when stored at room temperature for 12 months. In tests for bioavailability in the conjunctiva, the composition gave an area-under-the curve value of 12483 ng/g.hour compared with 7378 ng/g.hour for Cycloil (RTM; water-in-oil emulsion formulation of **cyclosporin** A as described in W09531211).

MECHANISM OF ACTION - None given.

USE - The use of (I) is claimed for treating dry kerato- conjunctivitis, Sjogren's syndrome, dry eye syndrome or chronic vernal kerato-conjunctivitis, or post-operative prophylaxis in kerato-plastic surgery. The active agents (a) have immunosuppressive and antiinflammatory activity.

ADVANTAGE - Inclusion of (b) and (c) solubilizes the active agent (a), improves the bioavailability in the conjunctiva, cornea and lachrymal gland and improves the ocular tolerance. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A03-A00A; A05-H01B; A12-V01; B02-C01; B04-C02E;  
B04-C03D; B14-C03; B14-G02; B14-N03  
TECH UPTX: 20020123

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (a) is **cyclosporin A**. (b) has average molecular weight at least 1300000 (preferably 1300000-3000000) Daltons, and is in the form of an alkali metal or alkaline earth metal salt, especially the sodium salt.

L139 ANSWER 53 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2002-011896 [02] WPIX  
DOC. NO. CPI: C2002-003137  
TITLE: High water content water-in-oil **emulsion** creams containing e.g. pharmaceuticals together with lecithin and short-chain di- or tri-ols are sterile filtered to give stable products with reduced secondary effects.  
DERWENT CLASS: B04 D21 E11  
INVENTOR(S): HEIDE, P E  
PATENT ASSIGNEE(S): (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
DE 10015463	A1	20011018	(200202)*		4	A61K009-06	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10015463	A1	DE 2000-10015463	20000329

PRIORITY APPLN. INFO: DE 2000-10015463 20000329

INT. PATENT CLASSIF.:

MAIN: A61K009-06

SECONDARY: A61K007-48; A61K031-573; A61K038-13

BASIC ABSTRACT:

DE 10015463 A UPAB: 20020109

NOVELTY - A cream in the form of a high water content water-in-oil (W/O) **emulsion** consisting of:

- (a) lecithin with a content of phosphatidyl-choline and -ethanolamine,
  - (b) a short-chain di- or tri-ol, (c) an oil,
  - (d) water and
  - (e) an active component
- is sterile filtered.

ACTIVITY - Antiallergenic; Immunosuppressive; Ophthalmological

MECHANISM OF ACTION - None given in the source material.

USE - E.g. for application **cyclosporin** to the skin as an immunodepressive, or to the **eyes** to treat them after corneal grafting. Other preferred actives include hydrocortisone acetate and betamethason, while creams containing other

glucocorticosteroids or antimycotics, antiseptics, thiocarbamates, hormones or cytostats are disclosed.

ADVANTAGE - The cream is easily made and does not show the secondary activity associated with the preservatives used in the prior-art to improve cream stability. Component (a) forms stable hydrate shells in water. The cream is also non-allergenic. Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: B01-C01; B04-B01B; B04-C01C; B05-B01P; B10-C04E;  
B10-E04C; B14-G02; B14-G02A; B14-N03; D08-B09A; E01;  
E05-G09D; E10-C04H; E10-E04H

TECH UPTX: 20020109

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition comprises:

- (a) (especially soya) lecithin made up of 60-80 wt.% phosphatidyl-choline at 5-20 wt.%;
- (b) propanediol or glycerol at 10-20 wt.%;
- (c) natural oils with high linoleic or linolenic acid content (especially maize germ-, sunflower-, thistle- or neutral-oil) at 30-50 wt.%; (d) water at 40-50 wt.%; and
- (d) cyclosporin, hydrocortisone acetate or betamethasone at up to 2 wt.%.

Also present is an antioxidant at up to 0.05 wt.%, especially 0.02% vitamin E and 0.01% ascorbyl palmitate.

Preferred Process: The filter has a pore size of 0.45 microns.

L139 ANSWER 54 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2000-037292 [03] WPIX  
 DOC. NO. CPI: C2000-009539  
 TITLE: Alleviating dry eye related symptoms in dry eye patients and contact lens wearers.  
 DERWENT CLASS: A96 B04  
 INVENTOR(S): DING, S; OLEJNIK, O; REIS, B L  
 PATENT ASSIGNEE(S): (ALLR) ALLERGAN  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 5981607	A	19991109	(200003)*		13	A61K047-12	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5981607	A	US 1998-8924	19980120

PRIORITY APPLN. INFO: US 1998-8924 19980120  
INT. PATENT CLASSIF.:

MAIN: A61K047-12  
SECONDARY: A61K047-14; A61K047-34

BASIC ABSTRACT:

US 5981607 A UPAB: 20000118  
NOVELTY - Alleviating dry eye related symptoms in dry eye patients and contact lens wearers comprises ocular administration of an emulsion of a higher fatty acid glyceride (FAG), polysorbate 80 and Pemulen (RTM: polymeric emulsifier, carbomer 1342) in water, with no cyclosporin.

ACTIVITY - Antiinflammatory; antiallergic.

MECHANISM OF ACTION - None given.



USE - The method is used for alleviating dry eye related symptoms, e.g. in patients having immune mediated keratoconjunctivitis sicca or dry eye disease or dry eye symptoms of contact lens wearers.

ADVANTAGE - The composition is non-irritating with high comfort level and low irritation potential.

DESCRIPTION OF DRAWING(S) - The drawing shows a bar graph of subjective reports of Ocular dryness as a function of time following instillation of the emulsion.

Dwg.6/7

FILE SEGMENT: CPI  
 FIELD AVAILABILITY: AB; GI; DCN  
 MANUAL CODES: CPI: A12-V02A; B04-B01B; B04-B01C; B04-C03B; B04-C03D;  
 B10-E04C; B12-M03; B14-C03; B14-G02A;  
 B14-N03

TECH UPTX: 20000118

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The weight ratio of FAG to polysorbate 80 is 0.3 to 30. The FAG is castor oil or corn oil. A preferred composition comprises: castor oil 0.6255%, polysorbate 80 1%, Pemulen 0.05%, and glycerine 2.2%.

L139 ANSWER 55 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1999-519544 [44] WPIX  
 DOC. NO. CPI: C1999-151959  
 TITLE: Pharmaceutical composition containing cyclosporin  
 A suitable for topical administration for treating disorders of skin, mucosa and eyes.  
 DERWENT CLASS: B03 B04  
 INVENTOR(S): HEIDE, P E  
 PATENT ASSIGNEE(S): (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS; (HEID-I) HEIDE P  
 E  
 COUNTRY COUNT: 25  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
DE 19810655	A1	19990916	(199944)*		6	A61K038-13	
EP 945136	A1	19990929	(199945)	GE		A61K038-13	
	R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
		RO SE SI					
EP 945136	B1	20051116	(200576)	GE		A61K038-13	
	R:	AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
DE 59912782	G	20051222	(200603)			A61K038-13	
ES 2248935	T3	20060316	(200622)			A61K038-13	
EP 945136	B9	20060524	(200635)	GE		A61K038-13	
	R:	AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19810655	A1	DE 1998-1010655	19980312
EP 945136	A1	EP 1999-104009	19990312
EP 945136	B1	EP 1999-104009	19990312
DE 59912782	G	DE 1999-512782	19990312
		EP 1999-104009	19990312
ES 2248935	T3	EP 1999-104009	19990312
EP 945136	B9	EP 1999-104009	19990312

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 59912782	G Based on	EP 945136
ES 2248935	T3 Based on	EP 945136

PRIORITY APPLN. INFO: DE 1998-19810655 19980312  
 INT. PATENT CLASSIF.:

MAIN: A61K038-13  
 SECONDARY: A61K009-107; A61P017-00; A61P037-08

BASIC ABSTRACT:

DE 19810655 A UPAB: 19991026

NOVELTY - Pharmaceutical composition containing cyclosporin A (I) is in the form of an oil-in-water nano emulsion.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) use of a pharmaceutical composition containing (I) in a form suitable for topical administration for treating skin disorders;

(2) use of a pharmaceutical composition containing (I) in a form suitable for topical administration for treating allergies;

(3) preparation of the nano emulsion composition by dissolving (I) in an oil phase, adding part of the aqueous phase, stirring, adding the rest of the aqueous phase, sonicating the mixture, and sterilizing the product by filtration.

ACTIVITY - Immunosuppressant.

MECHANISM OF ACTION - Inhibitor of interleukin release.

USE - The composition is useful for (a) treating disorders of the skin, oral mucosa or genital mucosa; lichen ruber; neurodermatitis, especially in the region of the eyes; allergies, especially in the region of the eyes; (b) prophylactic and/or therapeutic treatment of the eyes; (c) inhibiting transplant rejection, preferably in the region of the eyes (e.g. corneal transplant rejection).

ADVANTAGE - The nanoemulsion contains (I) in highly dispersed form, is readily distributed over tissues and absorbed into tissues, has good compatibility with skin and eyes, and contains non organic solvents.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B02-C01; B04-B01B; B05-B01P; B10-E04C;  
 B12-M03; B14-G02; B14-L07; B14-N03; B14-N05;  
 B14-N17

TECH UPTX: 19991026

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The nanoemulsion has a droplet size below 500 nm. The composition comprises 0.1-10 (preferably 1-3, especially 2) wt.% (I); 0.1-20 (preferably 1-10, especially 5) wt.% phospholipid, especially lecithin; 10-40 (preferably 20-30, especially 23) wt.% triglycerides, preferably medium-chain triglycerides; and physiological saline, optionally containing preservatives and thickeners. The total lipid content is 1-50 (preferably 20-30) wt.%.

L139 ANSWER 56 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 1990-134228 [18] WPIX

DOC. NO. CPI: C1990-058873

TITLE: Topical ophthalmic compsn. - contains cyclosporin with a vegetable oil and a petroleum jelly.

DERWENT CLASS: B03 P32

INVENTOR(S): PEEPLES, R E

PATENT ASSIGNEE(S): (SANO) SANDOZ SA; (PEEP-I) PEEPLES R E; (SANO) SANDOZ LTD; (SANO) SANDOZ AG

COUNTRY COUNT: 21  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG MAIN IPC
GB 2224205	A	19900502	(199018)*		28
DE 3935517	A	19900503	(199019)		
PT 92120	A	19900430	(199022)		
NL 8902657	A	19900516	(199023)		
AU 8943715	A	19900503	(199024)		
FR 2638089	A	19900427	(199024)		
CA 2001502	A	19900426	(199025)		
NO 8904266	A	19900521	(199026)		
SE 8903583	A	19900427	(199026)		
DK 8905312	A	19900427	(199028)		
JP 02164830	A	19900625	(199031)		
FI 8905064	A	19900427	(199032)		
HU 52394	T	19900730	(199035)		
LU 87613	A	19910507	(199127)		
ZA 8908140	A	19910626	(199131)		
ES 2020032	A	19910716	(199133)		
CH 679210	A	19920115	(199208)		
GB 2224205	B	19920415	(199216)		
BE 1003578	A4	19920428	(199224)	30	A61K
IT 1237824	B	19930618	(199347)		A61K000-00
IL 92120	A	19940227	(199419)		A61K037-02
PH 28428	A	19940905	(199838)		A61K031-195

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2224205	A	GB 1988-24040	19881025
DE 3935517	A	DE 1989-3935517	19891025
NL 8902657	A	NL 1989-2657	19891026
FR 2638089	A	FR 1989-14023	19891024
JP 02164830	A	JP 1989-276174	19891025
ZA 8908140	A	ZA 1989-8140	19891026
ES 2020032	A	ES 1989-3619	19891026
GB 2224205	B	GB 1989-24040	19891025
BE 1003578	A4	BE 1989-1138	19891024
IT 1237824	B	IT 1989-48485	19891026
IL 92120	A	IL 1989-92120	19891025
PH 28428	A	PH 1989-39416	19891026

PRIORITY APPLN. INFO: US 1988-262866 19881026

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K013-40; A61K031-195; A61K037-02  
 SECONDARY: A61F009-00; A61K009-06; A61K031-39; A61K047-00  
 ADDITIONAL: C07K007-64

BASIC ABSTRACT:

GB 2224205 A UPAB: 19930928

Topical ophthalmic compsns comprise a **cyclosporin**, a vegetable oil (1) and a petroleum jelly (2) (pref white petrolatum). Compsn may also cont **emulsifiers** (3) and preserving/antimicrobial agents (4).

USE/ADVANTAGE - Compsns are used for treatment of conditions of the **eye** and surrounding area, esp autoimmune diseases, uveitis, corneal transplant, keratoconjunctivitis sicca. Compsns have rapid delivery to anterior and

posterior regions of the **eye**, cause little discomfort to patients, have convenient application rate, and low systemic involvement.

0/7

FILE SEGMENT: CPI GMPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: B04-B01C1; B04-B01C3; B04-C01C; B12-D07; B12-L04  
ABEQ GB 2224205 B UPAB: 19930928

An ophthalmic compsn. comprising a **cyclosporin** as active ingredient and comprising (1) an ophthalmically acceptable vegetable oil and (2) an ophthalmically acceptable petroleum jelly as carrier medium. \*\*\* ()

L139 ANSWER 57 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1986-335072 [51] WPIX  
DOC. NO. CPI: C1986-145258  
TITLE: **Eye** drops - composed of lipid microspheres containing remedies for **eye** troubles.  
DERWENT CLASS: B05  
PATENT ASSIGNEE(S): (MIZU-I) MIZUSHIMA H  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
JP 61249918	A	19861107	(198651)*		4		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 61249918	A	JP 1985-90426	19850426

PRIORITY APPLN. INFO: JP 1985-90426 19850426

INT. PATENT CLASSIF.: A61K009-10

BASIC ABSTRACT:

JP 61249918 A UPAB: 19930922

Any remedy for an **eye** trouble can be used, i.e., corticosteroid, **cyclosporin**, antibiotics, non-steroid anti-inflammatory drugs, remedies for cataract, remedies for glaucoma, etc..

LMS is produced conventionally except that the remedies are added in the course of production. Soy bean oil is pref. as the oil. Lecithin is pref. as the **emulsifier**. The oil, the **emulsifier** and the remedy are mixed and heated at 30-80 deg.C. The mixture is homogenised with homogeniser, sterilised water is added and the mixt. is homogenised again. Thus obtained LMS is 0.1-1.0 micron in radius and is very stable for a long time. The **eye** drops are used several times a day. The **eye** drops have no toxicity other than the side effect specific to the remedies contained in the them.

USE/ADVANTAGE - Continuous absorption and action to **eye** tissues without side effect is possible. 0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB  
MANUAL CODES: CPI: B12-L04; B12-M07; B12-M10A; B12-M11

L139 ANSWER 58 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2006:606158 HCAPLUS Full-text  
DOCUMENT NUMBER: 145:130749

TITLE: Ophthalmic preparation containing tetrandrine and use thereof in treating ophthalmic diseases  
 INVENTOR(S): Hu, Shixing; Xu, Yangui  
 PATENT ASSIGNEE(S): Peop. Rep. China  
 SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 25 pp.  
 CODEN: CNXXEV  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Chinese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1785192	A	20060614	CN 2004-10093862	20041208
PRIORITY APPLN. INFO.:			CN 2004-10093862	20041208

ED Entered STN: 23 Jun 2006

AB The ophthalmic preps. (eyedrop, ointment) is composed of tetrandrine 0.001-2, synergistic drugs 0-5, excipient 93-99.999, metal ion complexing agent (disodium edetate) 0-5, isotonic regulator (sodium chloride) 0-10%, solubilizer (0.1-2 M HCl) 0.05-50 mL, thickening agent (hydroxymethyl cellulose) 0-5, cuticle lytic agent (borneol) 0-5, and antioxidant (sodium pyrosulfite) 0-5%, resp. Excipient in eyedrop is injection water; excipient in ointment is wool grease 0-20, paraffin oils 0-20, sodium Et cellulose 0.1-10, and addnl. vaseline to 1000 g. The synergistic drug is antimicrobial, such as erythrocin, kanamycin, gentamicin, amikacin, tobramycin, sisomycin, netilmicin, micronomicin, isepamicin, astromicin, etimicin, neomycin, spectinomycin, tetracycline, paromomycin, doxycycline, minocycline, sulfacetamide sodium, norfloxacin, ofloxacin, enoxacin, ciprofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, fleroxacin, moxifloxacin, rifampicin, metronidazole, tinidazole or cefoperazone; antiviral drugs, such as acyclovir, ganciclovir, valaciclovir or ribavirin; hormone drugs, such as dexamethasone phosphate, fluocinolone, beclometasone, etc.; vitamin, such as vitamin B1, vitamin B2, vitamin B6, vitamin B12 or vitamin C, niacinamide or folic acid; anti-inflammatory drug, such as indometacin, ibuprofen, meloxicam, piroxicam, diclofenac sodium, paracetamol or nimesulide; antianaphylactic drug, such as chlorphenamine, diphenhydramine, tripeleminamine, etc.; immunoregulatory drug, such as \*\*\*\*, ciclosporin, Tripterygium glycosides, tacrolimus, etc.; amino acids; microcirculation-improving nicotinic acid, inositol hexanicotinate or vinpocetine; Chinese medicine active ingredient, such as dipyrindamole, puerarin, ligustrazine, allitridin, berberine, isatisroot, fibrauretin, houttuynine, andrographolidume or Sophora flavescens alkaloids. The antioxidant is sodium sulfite, sodium thiosulfate, methionine, thiourea, BHA, BHT, CDGA, tocopherol; isotonic regulator is boric acid, sodium dihydrogen phosphate, disodium hydrogen phosphate or glucose; thickening agent is Me cellulose, Et cellulose, etc.; cuticle lytic agent is menthol; tetrandrine is tetrandrine hydrochloride, tetrandrine sulfate, tetrandrine nitrate, tetrandrine phosphate, etc. Chlorhexidine, benzalkonium bromide, phenylhydrargyric nitrate, phenylhydrargyric acetate, chlorbutol, thiomersalate, mercuric oxycyanide, paraben, benzyl carbinol, sorbic acid, benzoic acid or domiphen are added in medical formulation while using non-antibiotic drugs. The ophthalmic preparation is used for treating chorioretinitis, ceratitis, anaphylactic ophthalmic disease, glaucoma and cataract, proliferative lesion of retinal vitreous body, etc.

L139 ANSWER 59 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1355515 HCAPLUS Full-text

DOCUMENT NUMBER: 144:74885

TITLE: Pharmaceutical compositions containing polyunsaturated fatty acid in combination with immunosuppressive