

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**

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
- ☐ Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
- ☒ 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)*
- ☐ English Translation Document *(if applicable)*

19587 U.S. PTO
10/927857

- ☐ Information Disclosure Statement/PTO-1449
☐ Preliminary Amendment
☒ Acknowledgment postcard
☒ Certificate of Mailing by Express Mail
☒ APPLICATION DATA SHEET
☐ REQUEST FOR NON-PUBLICATION

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



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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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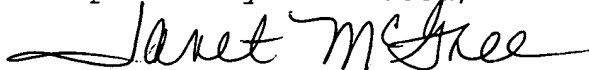
Date of Deposit: AUGUST 27, 2004

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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THE ENCLOSED PATENT APPLICATION OF ACHEAMPONG ET AL. IS
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SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

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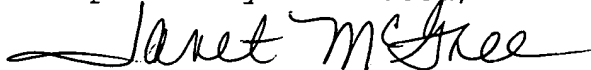
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METHODS OF PROVIDING THERAPEUTIC EFFECTS
USING CYCLOSPORIN COMPONENTS

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,
lacrima 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
15 than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

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 kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

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

administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, 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.

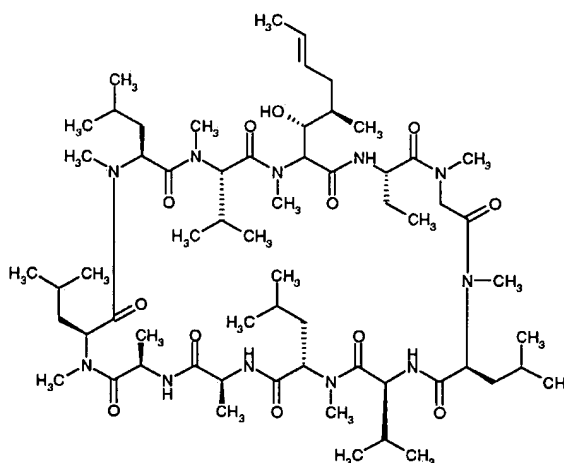
One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3 μ 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.

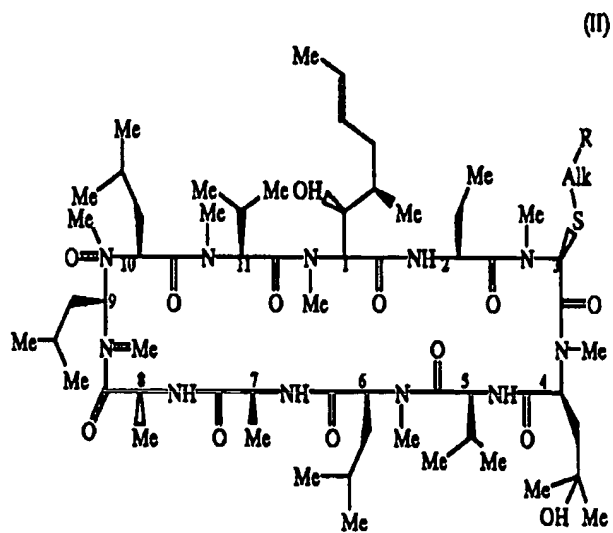
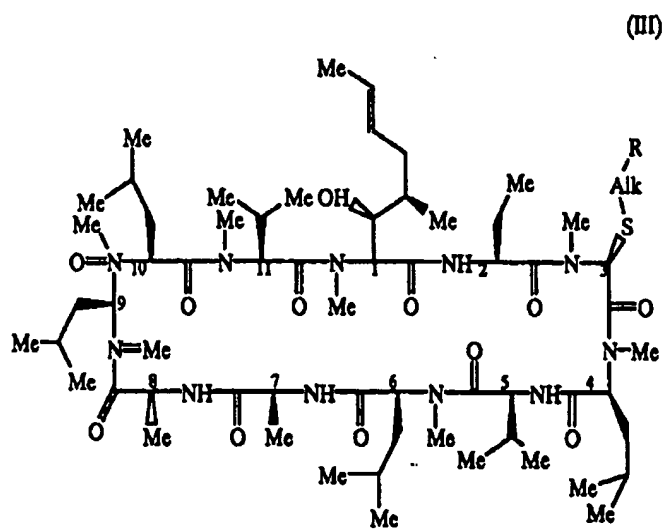
The chemical structure for cyclosporin A is represented by Formula 1

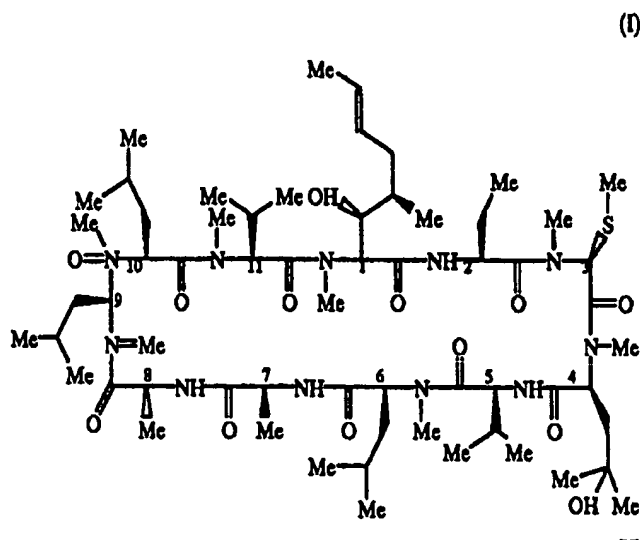
Formula I



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

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

Formula IIFormula III

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 amphorteric 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
5 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
10 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
15 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%
20 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
25 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
30 of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in

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

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

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

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

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

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

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

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

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

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

The presently useful compositions may be produced using conventional and well known methods useful in

producing ophthalmic products including oil-in-water emulsions.

5 In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the
10 highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the
15 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
20 components are dissolved in the oily phase.

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

emulsion may be already formed at this point.

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
10 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
15 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
20 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.

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

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

EXAMPLE 1

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

5	<u>Composition I</u>		<u>Composition II</u>
	wt%		wt%
	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:

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) ☒ 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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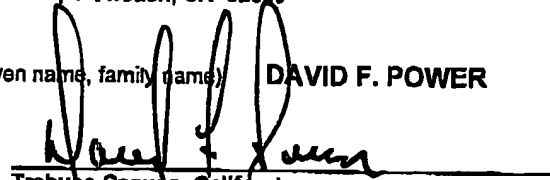
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Application Information

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

Representative Information

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Registration Number Four::	Kenton R. Mullins.....	36,331
Registration Number Five::	Jo Anne M. Ybaben.....	42,243
Registration Number Six::	Linda Allyson Fox.....	38,883
Registration Number Seven::	Greg S. Holrigel, 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

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper for
Application Serial No. 10/927,857 is being
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on the date shown below.

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
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) ☒ 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 Allyson Fox, Reg. No. 38,883; and Greg S. Holtrigel, Reg. No. 45,374.


Address all telephone calls to
Address all correspondence to

Frank J. Uxa - Telephone: 949-450-1750
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**

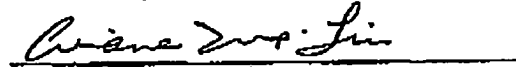
Inventor's signature
Residence
Post Office Address


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^{LLC} 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

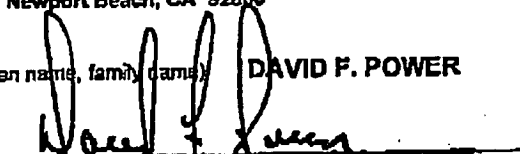
Date

Citizenship U.S.A.

8/12/04

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

Inventor's signature
Residence
Post Office Address


Trabuco Canyon, California
28335 Quiet Hill Lane
Trabuco Canyon, CA 92679-1131

Date

Citizenship U.S.A.

8/12/04

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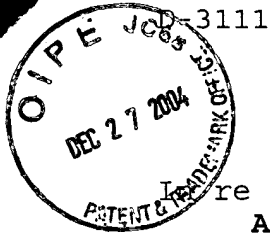
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

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)

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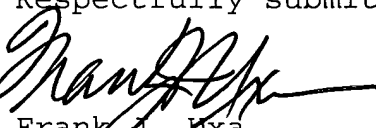
December 22, 2004
Date
Janet McGhee

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

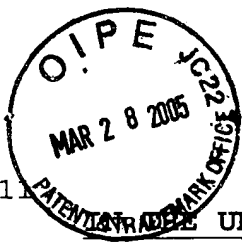
FJUxa/ac

Form PTO-1449 INFORMATION DISCLOSURE CITATION IN AN APPLICATION (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
	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</i> , Plenum Press, New York & London, ©1998, pp. 1001-1004.				
	AB	Acheampong et al, "Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs," <i>Curr Eye Res</i> , Feb 1999, 18(2):91-103b.				
	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</i> , Plenum Press, New York & London, ©1998, pp. 991-5.				
	AD	Brewster et al, "Enhanced Delivery of Ganciclovir to the Brain through the Use of Redox Targeting," <i>Antimicrobial Agents and Chemotherapy</i> , April 1994, 38(4):817-823.				
	AE	Brewster et al, "Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl- β -cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions," <i>J Pharm Sci</i> , March 1997, 86(3):335-9.				
EXAMINER			DATE CONSIDERED			
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			Docket No.: D-3111		Application No.: 10/927,857	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION <small>(Use several sheets if necessary)</small>			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
	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.			
FOREIGN PATENT DOCUMENTS						
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						YES NO
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)						
	AA	Brewster et al, "Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl- β -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					
EXAMINER			DATE CONSIDERED			
<small>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.</small>						

Form PTO-1449			Docket No.: D-3111		Application No.: 10/927,857	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION <small>(Use several sheets if necessary)</small>			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
	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.			
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	AB					
	AC					
	AD					
	AE					
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	AG					
	AH					
EXAMINER			DATE CONSIDERED			
<small>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.</small>						

Form PTO-1449			Docket No.: D-3111		Application No.: 10/927,857	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION <small>(Use several sheets if necessary)</small>			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
	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.			
FOREIGN PATENT DOCUMENTS						
DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
					YES	NO
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)						
	AA					
	AB					
	AC					
	AD					
	AE					
	AF					
	AG					
EXAMINER			DATE CONSIDERED			
<small>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.</small>						



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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

0062

2006 10/03

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10/927,857

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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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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
L5 (      446)SEA FILE=BIOSIS ABB=ON  PLU=ON  POWER D?/AU
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L8 (    124285)SEA FILE=BIOSIS ABB=ON  PLU=ON  OIL
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L13 (      9)SEA FILE=BIOSIS ABB=ON  PLU=ON  ((L2 OR L3 OR L4 OR L5)) AND
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L14      9 SEA FILE=BIOSIS ABB=ON  PLU=ON  L12 OR L13
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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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'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/nd05/nd05_med_data_changes.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 <

>>> 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 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 <<<
'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))
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=> 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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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 (≥ 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 **cyclosporin 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-benzoyloxyquinoline (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)

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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)

L72 ANSWER 12 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

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 α 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, pharmacoeconomics
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 angiostatic steroids, 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, maloplasia 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, maloplasia 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, maloplasia 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																			
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	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
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	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, maloplasia 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. (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	
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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							
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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.

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

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OR PUPIL DISORDERS OR REFRACTIVE ERRORS OR RETINAL DISEASES
OR SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR
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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
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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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=> 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/nd05/nd05 med data changes.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,
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<http://www.stn-international.de/training center/patents/stn guide.pdf> <

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>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
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 <<<
'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

FILE 'BIOSIS' ENTERED AT 16:39:41 ON 02 OCT 2006

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PROCESSING COMPLETED FOR L137

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 ***ciclosporin*** 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 ciclosporin in the currently available formulation) and 30 patients whose ciclosporin 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 ***ciclosporin*** 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

CAS REGISTRY NO.: Pruritus: CI, chemically induced
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 (α -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 α -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, α -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), α -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, α -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 α -CD afforded the greatest CYA penetration of the cornea. We then tested 4 different concentrations of α -CD to determine the least toxic concentration. The concentrations were: 80, 40, 20 and 10 mg/ml. of α -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 α -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: Mevasseret 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.⁶** **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 $\mu\text{g/ml}$ to 30 $\mu\text{g/ml}$ 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:

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
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SOURCE: European Journal of Pharmaceutics and Biopharmaceutics,
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LANGUAGE: English

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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
 STN

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.
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 DOCUMENT TYPE: Article
 LANGUAGE: English
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 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

L139 ANSWER 19 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
 STN

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 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.
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 November 2-6, 1997. American Association of Pharmaceutical
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 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
 STN

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**)

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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
 antiviral 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: VCNA6
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) Adsorboteat; (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
Berlin, Campus Virchow Klinikum, Augustenburger Platz 1,
DE-13353 Berlin, Germany. eckart.bertelmann@charite.de

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 .COPYRG. 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.,
 Imperial College School of Medicine, Dept. of Viral
 Immunorheumatology, 1 Aspenlea Road, London W6 8LH, United
 Kingdom. p.venables@imperial.ac.uk
 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. Ocuser®), 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) Ocusert; (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
- téar 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

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ACCESSION NUMBER: 2003476197 EMBASE Full-text

TITLE: The potential of chitosan 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, pharmaceutics
 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, pharmaceutics
 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, pharmaceutics
 oligomer: DT, drug therapy
 oligomer: PD, pharmacology
 oligomer: CB, drug combination
 oligomer: PR, pharmaceutics
 tobramycin: DT, drug therapy
 tobramycin: PR, pharmaceutics
 tobramycin: CB, drug combination
 microsphere: CB, drug combination
 microsphere: PR, pharmaceutics
 aciclovir: CB, drug combination
 aciclovir: PR, pharmaceutics
 drug carrier: PD, pharmacology
 drug carrier: PR, pharmaceutics
 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, pharmaceutics
 ofloxacin: CB, drug combination
 ofloxacin: PR, pharmaceutics
 ofloxacin: CR, drug concentration
 liposome: CB, drug combination
 liposome: PR, pharmaceutics

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

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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

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].

EFFECTO 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/ μ 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 mm² respectively, in controls and 4.9, 5.3 and 5.2 mm² 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

L139 ANSWER 38 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

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

L139 ANSWER 39 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

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
 sjogren syndrome: TH, therapy
 sjogren 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.; Piergiacomini 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

*sjogren syndrome: DT, drug therapy

*sjogren syndrome: TH, therapy

*sjogren 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, mucolipidoses, 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.

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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)

COUNTRY COUNT: LAMBERT G; (RABI-I) RABINOVICH-GUILATT L
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 periorcularly 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 impeding agents such as colchicines, vincristine, cytochalasin B and related compounds; carbonic anhydrase inhibitors such as acetazolamide, methazolamide, dichlorophenamide, 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, imipenem; 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, lomustine, 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 tetrahydrazoline; 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

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, tretinoin, 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, pentoxifylline, 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, lysine 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 antiinflammatory 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 antiinflammatory 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, phrilamine maleate, chlorpheniramine, tripeleminamine, 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, acetaminophen, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfeamic 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, tretinoin, 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, pentoxifylline, 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, lycine 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 entrostatically 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 entrostatically 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 entrostatically 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 WO9531211).

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, micromomicin, 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, tripeleennamine, 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