S($ 10/97)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No: **D-3111**

Total Pages in this Submission

22713 U.S.PTO 082704

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

19587 U.S.PTO 10/927857 082704

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

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

and invented by:

ACHEAMPONG ET AL

If a CONTINUATION APPLICATION, *check appropriate box an supply the requisite information:*
[ ]**Continuation** [ ]**Divisional** [ ]**Continuation-in-part (CIP)** of prior application No.:

Enclosed are **Application Elements**:

[X] Filing Fee

[X] Specification having **34** page(s) and including the following:

- [X] Title of the Invention
- [X] Cross References to Related Applications *(if applicable)*
- [X] Background of the Invention
- [X] Brief Summary of the Invention
- [ ] Description of the Drawings
- [X] Detailed Description
- [X] Claim(s) as Classified Below
- [X] Abstract of the Disclosure

[ ] __ Sheets of Drawings(s) (37 CFR 113) [ ] Formal [ ] Informal

[X] Oath or Declaration [X] Executed [ ] Unexecuted
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[X] Power of Attorney [X] Executed [ ] Unexecuted
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[X] 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

[X] 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)*

[ ] Information Disclosure Statement/PTO-1449 [ ] Copies of _ IDS Cited Reference(s)
[ ] Preliminary Amendment
[X] Acknowledgment postcard
[X] Certificate of Mailing by Express Mail
[X] APPLICATION DATA SHEET
[ ] REQUEST FOR NON-PUBLICATION

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)* [ ]					$ 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.
[X] The Commissioner is hereby authorized to charge and/or credit Deposit Account Number **01-0885** as described below.
  [X] Charge the amount of $1,098.00 as filing fee.
  [X] Credit any overpayment.
  [X] 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	)	

Express Mail Mailing Label No. EV 464416262 US

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,

Janet E. McGhee, Office of
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DOCKET NO.: D-3111

THE ENCLOSED PATENT APPLICATION OF ACHEAMPONG ET AL. IS BEING FILED IN ACCORDANCE WITH SECTION 37 CFR 1.10 BY EXPRESS MAIL AND SHOULD BE ACCORDED A FILING DATE

AUGUST 27, 2004

SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

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D-3111

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Related Application

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

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 therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

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

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

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

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

concentrations 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.

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.

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

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

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

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

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

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

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

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

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

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as

mixtures of two or more individual cyclosporins and derivatives thereof.

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.

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

Detailed Description

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

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

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.

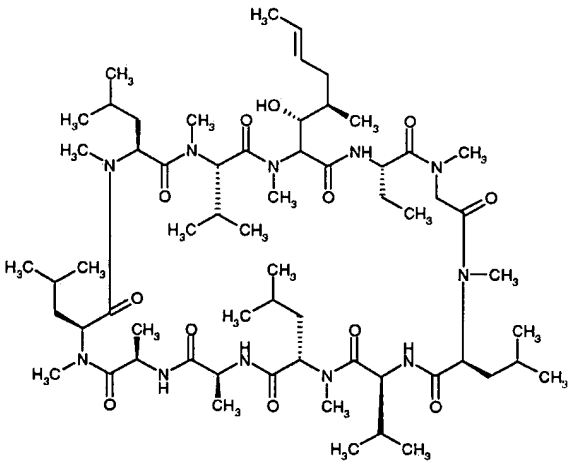
One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected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

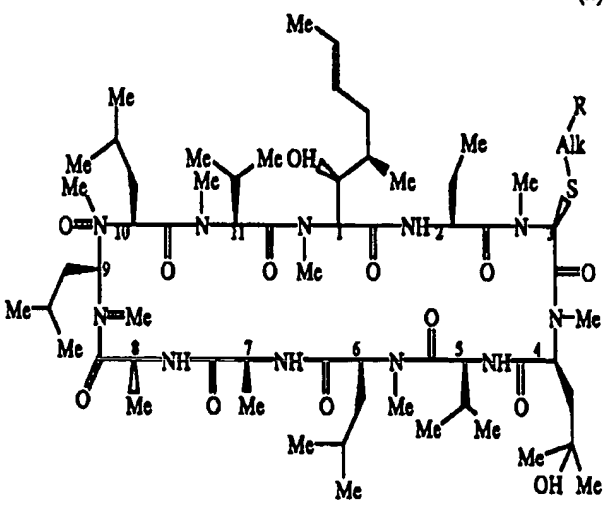


As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without 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:

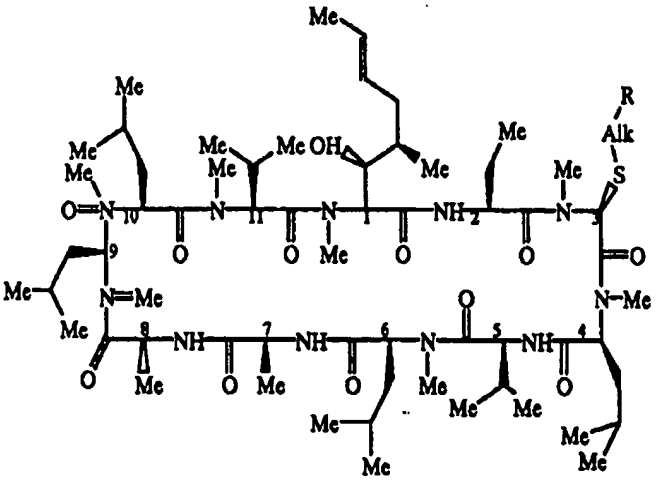
Formula II

(II)



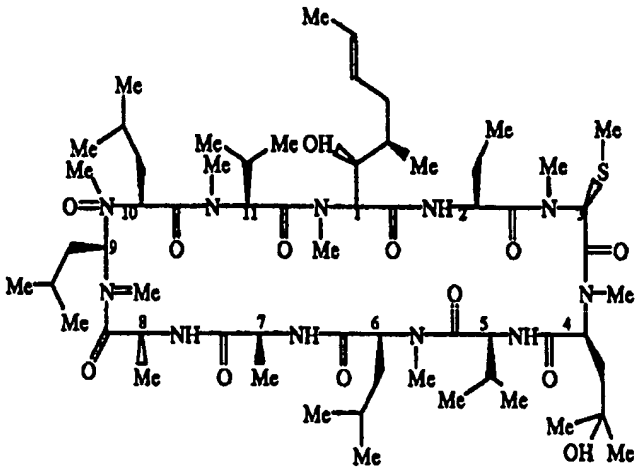
Formula III

(III)



Formula IV

(I)



wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $-NR_1R_2$ or $N(R_3)-(CH_2)-NR_1R_2$; wherein R_1, R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, 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 maintained in a substantially sterile condition.

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

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

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

compositions, and the like and mixtures thereof.

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

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

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

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

heparin
gucoaminoglycans
hyaluronic acid
chondroitin sulfate
dermatan sulfate
peptides and polypeptides
alginic acid
metal alginates
homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- vinylsulfonic acid
- metal vinylsulfonate
- amino acids, such as aspartic acid, glutamic acid and the like
- metal salts of amino acids
- p-styrenesulfonic acid
- metal p-styrenesulfonate
- 2-methacryloyloxyethylsulfonic acids
- metal 2-methacryloyloxethylsulfonates
- 3-methacryloyloxy-2-hydroxypropylsulonic acids
- metal 3-methacryloyloxy-2-hydroxypropylsulfonates
- 2-acrylamido-2-methylpropanesulfonic acids
- 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 Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are

commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

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

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

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

Ophthalmic demulcent components may be included in

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

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

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

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

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

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

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

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

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

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

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

producing ophthalmic products including oil-in-water emulsions.

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

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

emulsion may be already formed at this point.

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

The present oil-in-water emulsions preferably are thermodynamicaly 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:

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

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

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

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

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

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

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

While this invention has been described with respect

to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

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

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

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

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

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

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

6. The method of claim 1 wherein the blood of the

human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22. The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin component.

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

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

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

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

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

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

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

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

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

component.

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

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

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

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

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

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Abstract of the Disclosure

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

DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

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

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

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

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

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

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

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

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

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 36,510, Stephen Donovan, Reg. No. 33,433, Brent A. Johnson, Reg. No. 51,851, Dean G. Stathakis, Reg. No. 54,465, Frank J. Uxa, Reg. No. 25,612, Donald E. Stout, Reg. No. 34,493; Robert D. Buyan, Reg. No. 32,460; Kenton R. Mullins, Reg. No. 36,331; Jo Anne M. Ybaben, Reg. No. 42,243, Linda Allyson Fox, Reg. No. 38,683, 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...

Docket No. D-3111

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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 Three::	Robert D. Buyan.....	32,460
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. Hollrigel, 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
Registration Number Twelve::	Brent A. Johnson.....	51,851

Registration Number Thirteen::	Dean G. Stathakis.....	54,465

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		☐

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

SMALL ENTITY TYPE ☐			OR OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
XS 9=		OR	XS18=	288
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	1058

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	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)

*U.S. Government Printing Office: 2002 — 469-267/69033

D-3111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of:
Acheampong et al

Serial No. 10/927,857

Filed: August 27, 2004

Group Art Unit: 1636

Examiner: N/A

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 facsimile transmitted to the Patent and Trademark Office fax number 703-872-9306 on the date shown below.

Janet McGhee 11/12/04
Signature Date

LETTER

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

Dear Sir:

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

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

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

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (714) 450-1764

DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

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

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

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

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

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

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

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

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

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 38,510, Stephen Donovan, Reg. No. 33,433, Brent A. Johnson, Reg. No. 51,851, Dean G. Stathakis, Reg. No. 54,465, Frank J. Uxa, Reg. No. 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. Hellriegel, Reg. No. 45,374.

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

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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

Inventor's signature A Acheampong Date 8/12/04
Residence Irvine, California Citizenship U.S.A.
Post Office Address 16 Wintergreen
Irvine, CA 92604

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

Inventor's signature Diane Tang-Liu Date 8-12-2004
Residence Newport Beach, California Citizenship U.S.A.
Post Office Address 2515 Blackthorn Street
Newport Beach, CA 92660

BEST AVAILABLE COPY

Docket No. D-3111

Continued...

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

Inventor's signature
Residence Newport Beach, California
Post Office Address 36 Cervantes
Newport Beach, CA 92660

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

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

Inventor's signature
Residence Trabuco Canyon, California
Post Office Address 28335 Quiet Hill Lane
Trabuco Canyon, CA 92679-1131

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

1 FW

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: 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

December 22, 2004
Date

Janet McGee

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	TRANSLATION 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," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, 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," *Curr Eye Res, Feb 1999, 18(2):91-103b.*
	AC	Angelov et al, "Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, 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," *Antimicrobial Agents and Chemotherapy, 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, " *J Pharm Sci, 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 (Use several sheets if necessary)	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

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION 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," *J Pharm Sci, 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," *Ophthalmology, 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," *J Ocul Pharmacol Ther, 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," *Ophthalmology, May 2000, 107(5):967-74.*
	AE	
	AF	

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 (Use several sheets if necessary)	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.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	

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

	AA	
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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 (Use several sheets if necessary)	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.)

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	AD	
	AE	
	AF	
	AG	

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.

IFW

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: 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
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Alicia Curran

Commissioner for Patents
P.O. Box 1450
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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
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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
	2001/0036449 A1	11/2001	Garst			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

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

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	AE	
	AF	
	AG	
	AH	

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.

2006 10/03

10/927,857

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
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L4   (      4672)SEA FILE=BIOSIS ABB=ON  PLU=ON  CHANG J?/AU
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                  ((L6 OR L7)) AND L11
L14              9 SEA FILE=BIOSIS ABB=ON  PLU=ON  L12 OR L13


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=> 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
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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
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=> 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,
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http://www.stn-international.de/training_center/patents/stn_guide.pdf <

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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))

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

FILE 'BIOSIS' ENTERED AT 16:31:07 ON 02 OCT 2006
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FILE 'HCAPLUS' 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

Shindaebang-Dong, Tongjak-Gu, Seoul 1560-012, South Korea
SOURCE: Experimental Eye Research, (April, 1998) Vol. 66, No. 4, pp. 389-396. print.
CODEN: EXERA6. ISSN: 0014-4835.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jun 1998
Last Updated on STN: 24 Jun 1998

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

CONCEPT CODE: Pharmacology - General 22002
Sense organs - General and methods 20001
INDEX TERMS: Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
INDEX TERMS: Parts, Structures, & Systems of Organisms
cornea: sensory system
INDEX TERMS: Diseases
corneal haze: **eye** disease
INDEX TERMS: Chemicals & Biochemicals
collagen: type III, type IV, type VI;
cyclosporin A: topical administration;
synthetic inhibitor of metalloproteinase [SIMP]: topical administration
INDEX TERMS: Methods & Equipment
excimer laser photorefractive keratectomy: surgical method; immunohistochemistry: histochemical method; light microscopy: microscopy method; slit lamp examination: examination method
ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
REGISTRY NUMBER: **59865-13-3** (**cyclosporin A**)
81669-70-7 (METALLOPROTEINASE)

L72 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:105948 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600105839
TITLE: Cytochrome P450 3A expression and activity in the rabbit lacrimal gland: Glucocorticoid modulation and the impact on androgen metabolism.
AUTHOR(S): Attar, Mayssa [Reprint Author]; Ling, Kah-Hiing John; **Tang-Liu, Diane D.-S.**; Neamati, Nouri; Lee, Vincent H. L.
CORPORATE SOURCE: Allergan Pharmaceut Inc, Dept Pharmacokinet and Drug Metab, Irvine, CA 92612 USA
attar_mayssa@allergan.com
SOURCE: IOVS, (DEC 2005) Vol. 46, No. 12, pp. 4697-4706.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Feb 2006
Last Updated on STN: 8 Feb 2006

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

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

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

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

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

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

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

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

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

L72 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:236076 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000236076
TITLE: Blood concentrations of **cyclosporin A** (CsA) during twice-daily treatment of 0.05% and 0.1% **cyclosporine** ophthalmic emulsions in patients with moderate to severe keratoconjunctivitis sicca.
AUTHOR(S): Small, D. S. [Reprint author]; **Acheampong, A.** [Reprint author]; Reis, B. [Reprint author]; Stewart, W.; Berdy, G.; Epstein, R.; Foerster, R.; Forstot, L.; **Tang-Liu, D.** [Reprint author]
CORPORATE SOURCE: Allergan Inc, Irvine, CA, USA
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S69. print. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002
CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Sense organs - Pathology 20006
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Clinical pharmacology 22005
General biology - Symposia, transactions and proceedings 00520
INDEX TERMS: Major Concepts
Ophthalmology (Human Medicine, Medical Sciences); Pharmacology
INDEX TERMS: Diseases
keratoconjunctivitis sicca: **eye** disease, treatment
Keratoconjunctivitis Sicca (MeSH)
INDEX TERMS: Chemicals & Biochemicals
cyclosporin A: immunosuppressant-drug, blood concentrations, ophthalmic emulsions, twice-daily treatment
INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **59865-13-3** (**cyclosporin A**)

L72 ANSWER 9 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:540426 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799839629
TITLE: Preclinical safety of **cyclosporine** ophthalmic emulsion.
AUTHOR(S): Angelov, O.; Wiese, A.; Andersen, J.; Small, D.; **Acheampong**, **A.**; Yuan, Y.; Brar, B.
CORPORATE SOURCE: Allergan, Irvine, CA, USA
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp. 50.
Meeting Info.: VIth International Symposium on Sjogren's Syndrome. Avon, Connecticut, USA. October 15-18, 1997.
CODEN: JRHUA9. ISSN: 0315-162X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1997
Last Updated on STN: 12 Dec 1997
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Sense organs - General and methods 20001

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

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

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

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

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

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

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

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

ACCESSION NUMBER: 1997:540385 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799839588
TITLE: A dose-ranging clinical trial to assess the safety and efficacy of **cyclosporine** ophthalmic emulsion for the treatment of the ocular surface disease and inflammation associated with keratoconjunctivitis sicca (KCS).
AUTHOR(S): Donshik, P.; Reis, B. L.; Burk, C. T.; Stern, K. L.; **Acheampong, A.**
CORPORATE SOURCE: Allergan, Irvine, CA, USA
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp. 43.
Meeting Info.: VIth International Symposium on Sjogren's Syndrome. Avon, Connecticut, USA. October 15-18, 1997.
CODEN: JRHUA9. ISSN: 0315-162X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1997
Last Updated on STN: 12 Dec 1997
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Inflammation and inflammatory disease 12508
Pathology - Therapy 12512

Sense organs - General and methods 20001
Pharmacology - General 22002

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

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

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

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

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

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

ACCESSION NUMBER: 1996:206571 BIOSIS Full-text
DOCUMENT NUMBER: PREV199698762700
TITLE: Ocular absorption of **cyclosporine** from an aqueous emulsion: Comparison to other eyedrop formulations.
AUTHOR(S): **Acheampong, A.; Tang-Liu, D.;** Shackleton, M.; Lam, S.; Angelov, O.; Ding, S.
CORPORATE SOURCE: Allergan Inc., Irvine, CA, USA
SOURCE: Investigative Ophthalmology and Visual Science, (1996) Vol. 37, No. 3, pp. S1026.
Meeting Info.: 1996 Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 21-26, 1996.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 1996
Last Updated on STN: 2 May 1996
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Inflammation and inflammatory disease 12508
Pathology - Therapy 12512
Sense organs - General and methods 20001
Sense organs - Physiology and biochemistry 20004
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
Routes of immunization, infection and therapy 22100
Immunology - Immunopathology, tissue immunology 34508
INDEX TERMS: Major Concepts

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

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

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

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

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

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

ABSTRACT: Acute anterior uveitis is the most common form of uveitis. HLA-B27-associated acute anterior uveitis is a distinct clinical entity that has wide-ranging medical significance due to its ocular, systemic, immunologic, and genetic features. The association between HLA-B27 and the spectrum of HLA-B27-associated inflammatory diseases remains one of.the strongest HLA-disease associations known to date. This review examines acute anterior uveitis with particular focus on HLA-B27-associated acute anterior uveitis, including the epidemiology, immunopathology, association with HLA-B27 and its subtypes, clinical features, complications, prognosis, and potential new therapies such as anti-TNFα 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.

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

CAS REGISTRY NO.: (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

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

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, mylasis, 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 erythematosis, rheumatoid arthritis, and multiple sclerosis, maloplakia of the skin.
DERWENT CLASS: B04
INVENTOR(S): **POWER**, D; STERN, M E
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 1
PATENT INFORMATION:

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

APPLICATION DETAILS:

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

PRIORITY APPLN. INFO: US 2004-990054 20041115; US 2006-429050 20060505
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
BASIC ABSTRACT:
US2006199760 A UPAB: 20061002
NOVELTY - Treating a human or animal suffering from systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, comprising topically administering a **cyclosporine** component to the subject, is new.

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

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

MECHANISM OF ACTION - None given.

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

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

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

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

TECH UPTX: 20061002

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

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

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006105945	A1	20060518	(200636)*		9	A61K038-12
WO 2006055418	A1	20060526	(200636)	EN		A61K038-12

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

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

PRIORITY APPLN. INFO: US 2004-990055 20041115
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
SECONDARY: A61P001-00; A61P001-02; A61P001-04; A61P015-00; A61P015-02; A61P017-00; A61P035-00

BASIC ABSTRACT:
US2006105945 A UPAB: 20060607

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

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

MECHANISM OF ACTION - None given.

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

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

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-C01; B04-C01H; B12-M12N; B14-A01A; B14-E08; B14-E10; B14-H01K1; B14-N05; B14-N07
TECH UPTX: 20060607

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

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

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

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006105944	A1	20060518	(200636)*		8	A61K038-12
WO 2006055417	A2	20060526	(200636)	EN		A61K038-12

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA

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

APPLICATION DETAILS:

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

PRIORITY APPLN. INFO: US 2004-990054 20041115
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
BASIC ABSTRACT:
US2006105944 A UPAB: 20061002
NOVELTY - Treating an inflammatory bowel disease in a human or animal comprising topically administering a **cyclosporin** A component (I) (**cyclosporin** A and/or its salts) in a rectal suppository to a human or animal, is new.
ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.; Antiulcer; Dermatological; Immunosuppressive; Antiarthritic; Antirheumatic; Neuroprotective; Keratolytic; Antipruritic; Cytostatic.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - (I) is useful for the treatment of an inflammatory bowel disease (ulcerative colitis) (claimed). (I) is useful for the treatment of systemic lupus erythematosis, rheumatoid arthritis, multiple sclerosis, maloplakia of the skin, oral frictional hyperkeratosis, oral manifestations of autoimmune blistering disease, oral lichen planus, aphthous ulcers, nasal polyps, rhinosporiodosis, sinusitis, iritis, carcinoid lung, laryngitis and atrophic gastritis. (I) was tested for its ability to treat systemic lupus erythematosis in a patient. The results showed that (I) reduced the severity of the systemic lupus erythematosis.
ADVANTAGE - The method can be easily and effectively practiced by the prescribing physician and patient without causing substantial or undue patient stress. The method is effective to treat an inflammatory bowel disease.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01B; B04-C01H; B12-M08; B12-M12P; B14-C09B; B14-E08; B14-E10B; B14-E10C1; B14-G02D; B14-H01K3; B14-N04; B14-N05A; B14-N17; B14-S01
TECH UPTX: 20060607
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The administering step comprises topically administering (I) at or near a tissue area of the human or animal affected by the inflammatory bowel disease (preferably ulcerative colitis). Treating comprises reducing the severity of at least one symptom of the inflammatory bowel disease (preferably ulcerative colitis).

L72 ANSWER 19 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-054193 [06] WPIX
DOC. NO. CPI: C2006-020316
TITLE: Liquid, useful to treat dry eye disease, comprises a therapeutically effective concentration of a **cyclosporin** and a vitamin E tocopherol polyethylene glycol succinate.
DERWENT CLASS: A96 B05
INVENTOR(S): **CHANG, J N**; GRAHAM, R; TIEN, W L
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC

COUNTRY COUNT: 111
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2005277584	A1	20051215	(200606)*		5	A61K038-13
WO 2006001963	A1	20060105	(200606)	EN		A61K009-08

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

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

PRIORITY APPLN. INFO: US 2004-865638 20040609
INT. PATENT CLASSIF.:
MAIN: A61K009-08; A61K038-13
SECONDARY: A61K031-355; A61K047-22; A61P027-04
BASIC ABSTRACT:

US2005277584 A UPAB: 20060124

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

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

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

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

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A10-E07; A12-V01; B02-C01; B12-M07; B14-A01; B14-A02; B14-B02; B14-C03; B14-G01; B14-N03
TECH UPTX: 20060124

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

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

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

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


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


=> S L81 NOT L14
L134          8 L81 NOT L14

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

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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

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

=> D QUE L94
L82 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L83             SEL  PLU=ON  L82 1- CHEM :       38 TERMS
L84 (     74476)SEA FILE=EMBASE ABB=ON  PLU=ON  L83
L85 (    301867)SEA FILE=EMBASE ABB=ON  PLU=ON  EYE DISEASE+NT/CT
L86 (      5657)SEA FILE=EMBASE ABB=ON  PLU=ON  OIL/CT
L87 (     46238)SEA FILE=EMBASE ABB=ON  PLU=ON  D3.60.650./CT
L88 (    225955)SEA FILE=EMBASE ABB=ON  PLU=ON  L85/MAJ
L89 (        22)SEA FILE=EMBASE ABB=ON  PLU=ON  L88 AND L84 AND ((L86 OR L87))
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L90 (        17)SEA FILE=EMBASE ABB=ON  PLU=ON  L89 NOT PY>2004
L91 (       416)SEA FILE=EMBASE ABB=ON  PLU=ON  L84(L)TP/CT
L92 (        12)SEA FILE=EMBASE ABB=ON  PLU=ON  L91 AND L85 AND ((L86 OR L87))

L93 (         9)SEA FILE=EMBASE ABB=ON  PLU=ON  L92 NOT PY>2004
L94          21 SEA FILE=EMBASE ABB=ON  PLU=ON  L90 OR L93


=> S L94 NOT L30
L135        21 L94 NOT L30

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

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

=> D QUE L111
L95 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L96 (     36733)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EYE, DISEASE+OLD,NT/CT
L97 (     24550)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L98 (    388102)SEA FILE=HCAPLUS ABB=ON  PLU=ON  OILS+OLD,NT/CT
L99              SEL  PLU=ON  L95 1- CHEM :      38 TERMS
L100(     23233)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L99
L101(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L100 AND L96 AND L97 AND L98
L102(         4)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L97
L103(        17)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L98
L104(     28869)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EMULSIONS/CT
L105(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L104 AND L98

L106(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L104
L107(        20)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L101 OR L102 OR L103 OR L105
                OR L106)
L108(        19)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L107 AND PATENT/DT
L109(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L107 NOT L108
L110(        19)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L108 OR L109)) NOT (PRY>2004
                 OR PR>2004)
L111         18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L110 NOT LIPOSOMAL COCHLEATE/T
                I
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=> 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

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http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

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    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
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=> D QUE L133
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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))
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=> DUP REM L137 L134 L135 L138 L136
FILE 'MEDLINE' ENTERED AT 16:39:41 ON 02 OCT 2006

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PROCESSING COMPLETED FOR L137
PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L135
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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 keratoconjonctivite 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 ($P < or = 0.05$) 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
Pruritus: CI, chemically induced

CAS REGISTRY NO.: 2321-07-5 (Fluorescein); **59865-13-3 (Cyclosporine)**; 8001-25-0 (olive oil)
CHEMICAL NAME: 0 (Emulsions); 0 (Fluoresceins); 0 (Ophthalmic Solutions); 0 (Plant Oils)

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

1210-6.
Journal code: 7706534. ISSN: 0003-9950.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 9 Mar 1990
Last Updated on STN: 9 Mar 1990
Entered Medline: 1 Sep 1989

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

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

L139 ANSWER 15 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 3
ACCESSION NUMBER: 1990:113390 BIOSIS Full-text
DOCUMENT NUMBER: PREV199089062881; BA89:62881
TITLE: THE EFFECT ON THE CORNEA OF VARIOUS VEHICLES FOR **CYCLOSPORIN EYE** DROPS.
AUTHOR(S): ALBA R M JR [Reprint author]; KANAI A; TAKANO T; KOBAYASHI C; NAKAJIMA A; KURIHARA K; FUKAMI M
CORPORATE SOURCE: DEP OPHTHALMOL, JUNTENDO UNIV SCH MED, 3-1-3 HONGO, BUNKYO-KU, TOKYO 113, JAPAN

SOURCE: Folia Ophthalmologica Japonica, (1989) Vol. 40, No. 5, pp. 902-908.
CODEN: NGKYA3. ISSN: 0015-5667.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 21 Feb 1990
Last Updated on STN: 22 Feb 1990

ABSTRACT:We tested several solvents, possible vehicles for **Cyclosporin**, (CYA) as to which had the least corneal toxicity. They were: peanut ***oil*** , palm **oil**, polyoxyethylene castor **oil**, medium chain-length triglyceride **emulsion** (MCT) and alpha cyclo-dextrin (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: Mevaseret Zion, Israel
ASSIGNEE: Yissum Research Development, Jerusalem, Israel; Company of the Hebrew University of Jerusalem Novagali S.A.S., Evry, France
PATENT INFORMATION: US 6656460 20031202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 2 2003) Vol. 1277, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

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

NAT. PATENT. CLASSIF.:424780400

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

INDEX TERMS: Major Concepts
Methods and Techniques; Pharmacology

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

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

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

US005474979A

United States Patent [19]

Ding et al.

[11] Patent Number: 5,474,979

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

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

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

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

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

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

[51] **Int. Cl.**[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 medicated 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 μg/ml to 30 μg/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 prefcrably, 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

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 robert.gurny@pharm.unige.ch
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (November 2003) Vol. 56, No. 3, pp. 307-318. print. ISSN: 0939-6411 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2004
Last Updated on STN: 18 Feb 2004

ABSTRACT:Systemic administration of **cyclosporine A** (CsA) is commonly used in the treatment of local ophthalmic conditions involving cytokines, such as coreal 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.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002
CONCEPT CODE: Sense organs - Physiology and biochemistry 20004
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
INDEX TERMS: Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
INDEX TERMS: Parts, Structures, & Systems of Organisms
eye: sensory system
INDEX TERMS: Chemicals & Biochemicals
HCO-60-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; MYS-40-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; Tween 80-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; nonionic surfactants; **oil-cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; **oil** /water **emulsion-cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug
INDEX TERMS: Methods & Equipment
high performance liquid chromatography: liquid chromatography, measurement method; topical application: drug administration method
INDEX TERMS: Miscellaneous Descriptors
ocular distribution; pharmacokinetics

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

L139 ANSWER 19 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:104244 BIOSIS Full-text
DOCUMENT NUMBER: PREV199800104244
TITLE: **Cyclosporine** ophthalmic O/W **emulsion**: Formulation and **emulsion** characterization.
AUTHOR(S): Ding, Shulin; Olejnik, Orest
CORPORATE SOURCE: Pharmaceutical Sci., Research and Development, Allergan Inc., Irvine, CA 92612, USA
SOURCE: Pharmaceutical Research (New York), (Nov., 1997) Vol. 14, No. 11 SUPPL., pp. S41. print.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists. Boston, Massachusetts, USA. November 2-6, 1997. American Association of Pharmaceutical Scientists.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 1998
Last Updated on STN: 3 Mar 1998
CONCEPT CODE: Pharmacology - General 22002
Biochemistry studies - General 10060
Sense organs - General and methods 20001
Routes of immunization, infection and therapy 22100
General biology - Symposia, transactions and proceedings 00520
INDEX TERMS: Major Concepts
Pharmacology
INDEX TERMS: Chemicals & Biochemicals
cyclosporine: ophthalmic-drug, **eye** drop, formulation, ophthalmic **oil**-in-water **emulsion**, topical use
INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **59865-13-3Q** (**cyclosporine**)
63798-73-2Q (**cyclosporine**)

L139 ANSWER 20 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on 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-g h ml-1 for nanocapsules vs. 1650 and 1300 mu-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-g h ml-1 for nanocapsules vs. 1650 and 1300 mu-g h ml-1 for the **emulsions**), a slower clearance from the blood and a reduced uptake by organs rich in reticuloendothelial cells (liver AUC = 22% of blood AUC for nanocapsules vs. 189% and 311% for the ***emulsions***). Concentration in the kidneys was lower with nanocapsules (kidneys AUC = 9% of blood AUC for nanocapsules vs. 34% and 92% for the ***emulsions***), indicating that nanocapsules, in addition to allowing an increased bioavailability, also bear some promise at reducing the nephrotoxic adverse reactions of **cyclosporin A**.

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

INDEX TERMS: Major Concepts
Pharmacology

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORIN

INDEX TERMS: Miscellaneous Descriptors
BIOAVAILABILITY; IMMUNOSUPPRESSANT-DRUG; NANOENCAPSULATED RADIOLABELLED **CYCLOSPORIN**; OPHTHALMIC APPLICATION; OPHTHALMIC-DRUG; PERORAL DELIVERY; PHARMACEUTICAL FORMULATION; PHARMACOKINETICS; PHARMACOLOGY; TISSUE CONCENTRATION

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

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

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

L139 ANSWER 22 OF 73 EMBASE

ACCESSION NUMBER: 2004467671 EMBASE Full-text
TITLE: The economic burden of dry eye: A conceptual framework and preliminary assessment.
AUTHOR: Reddy P.; Grad O.; Rajagopalan K.
CORPORATE SOURCE: P. Reddy, Abt Associates Inc., 55 Wheeler Street,

Cambridge, MA 02138, United States.
prabashni_reddy@abtassoc.com
SOURCE: Cornea, (2004) Vol. 23, No. 8, pp. 751-761. .
Refs: 84
ISSN: 0277-3740 CODEN: CORNDB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2004
Last Updated on STN: 19 Nov 2004
ABSTRACT: Purpose: To develop a conceptual framework for analyzing the economic burden of dry eye and a preliminary assessment of key factors that contribute to that burden. Methods: The MEDLINE database was searched from 1966 to May 2003 combining the term "dry eye" with various economic terms. In addition, individual interviews with a panel of clinicians were conducted to provide additional insight on resource use. Results: Direct resource utilization among dry eye sufferers includes healthcare professional visits, nonpharmacological therapies, pharmacological treatments, and surgical procedures, with the latter 2 categories being the major cost drivers. Complementary and alternative medicine (CAM) therapies are a newly recognized component of the dry eye economic burden. There is wide variation in patterns of diagnosis and treatment, but current therapies are not universally effective. Given the prevalence of the condition, indirect costs may be large. Utilization of pharmacological therapies, especially those other than tear replacements, the extent of CAM use, cost of complications of surgical procedures, and indirect costs are unknown. The natural history and probability that patients will transition between therapies, based on underlying disease severity, need to be elucidated. Conclusions: Dry eye is a prevalent condition with the potential for a high economic burden; additional studies are needed to further characterize the economic impact.

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

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

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

CHEMICAL NAME: Af 2975

L139 ANSWER 23 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

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: VCNAA6
PUBLISHER IDENT.: S 0195-5616(03)00187-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
ENTRY DATE: Entered STN: 13 May 2004
Last Updated on STN: 13 May 2004
CONTROLLED TERM: Medical Descriptors:
*tear film
***lacrimal gland disease: DT, drug therapy**
***lacrimal gland disease: ET, etiology**
clinical feature
diagnostic procedure
treatment outcome
lacrimal gland
goblet cell
nictitating membrane
meibomian gland
ophthalmology
veterinary medicine
drug tissue level
drug blood level
drug structure
lacrimation
dry eye: DT, drug therapy
nonhuman
review
CONTROLLED TERM: Drug Descriptors:
*immunomodulating agent: AN, drug analysis
*immunomodulating agent: CM, drug comparison
*immunomodulating agent: CR, drug concentration
*immunomodulating agent: DT, drug therapy
*immunomodulating agent: TO, drug toxicity
*immunomodulating agent: PD, pharmacology
*immunomodulating agent: TP, topical drug administration
*cholinergic receptor stimulating agent: CB, drug combination
*cholinergic receptor stimulating agent: DT, drug therapy
*cholinergic receptor stimulating agent: TO, drug toxicity
*cholinergic receptor stimulating agent: PD, pharmacology
*cholinergic receptor stimulating agent: PO, oral drug administration

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

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

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

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

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

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

L139 ANSWER 24 OF 73 EMBASE

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, Universitatsmedizin 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.

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
Sjoegren 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, pharmaceutics
*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, pharmaceutics
*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, pharmaceutics
*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, pharmaceutics

*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, pharmaceutics
macrolide: PK, pharmacokinetics
macrolide: PD, pharmacology
macrolide: TP, topical drug administration
amphotericin B: PR, pharmaceutics
chloramphenicol: PR, pharmaceutics
carbonate dehydratase inhibitor: PR, pharmaceutics
nonsteroid antiinflammatory agent: PR, pharmaceutics
diclofenac: PR, pharmaceutics
thalidomide: PR, pharmaceutics
liposome: PR, pharmaceutics
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, pharmaceutics
oligosaccharide: PR, pharmaceutics
eye drops: PR, pharmaceutics
eye drops: TP, topical drug administration
eye ointment: PR, pharmaceutics
eye ointment: TP, topical drug administration
chitosan: PR, pharmaceutics
chitosan: TP, topical drug administration
water oil cream: PR, pharmaceutics
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

L139 ANSWER 25 OF 73 EMBASE

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@mclink.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.

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, pharmaceutics
  olive oil: CB, drug combination
  olive oil: DT, drug therapy
  olive oil: PR, pharmaceutics
castor oil: CB, drug combination
castor oil: DT, drug therapy
castor oil: PR, pharmaceutics
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

L139 ANSWER 26 OF 73 EMBASE

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 cemiveline, 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.

CONTROLLED TERM: Medical Descriptors:
***Sjoegren syndrome: DI, diagnosis**
***Sjoegren syndrome: DT, drug therapy**
***Sjoegren 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
bioxtra

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; Bioxtra; Oralbalance; Saliva orthana; Luborant; Glandosane; Ilube; Lubri tears; Lacri lube; Geltears; Viscotears; Liquifilm; Sno tears; Tears naturale

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ACCESSION NUMBER: 2004377151 EMBASE Full-text

TITLE: [Biological availability of ophthalmic preparations 2. Ophthalmic therapeutic systems].
BIOLOGICKA DOSTUPNOST OCNICH LEKU 2. OCNI TERAPEUTICKE

SYSTEMY.

AUTHOR: Masteikova R.; Chalupova Z.; Savickas A.
CORPORATE SOURCE: R. Masteikova, Palackeho 1/3, 612 42 Brno, Czech Republic. masteikovar@vfu.cz

SOURCE: Ceska a Slovenska Farmacie, (2004) Vol. 53, No. 5, pp. 211-218. .
Refs: 122
ISSN: 1210-7816 CODEN: CSLFEK
COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
012 Ophthalmology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: Czech
SUMMARY LANGUAGE: English; Czech
ENTRY DATE: Entered STN: 24 Sep 2004
Last Updated on STN: 24 Sep 2004

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

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

ganciclovir: DT, drug therapy
ganciclovir: PR, pharmaceutics
corticosteroid: DT, drug therapy
corticosteroid: PR, pharmaceutics
fluocinolone: DT, drug therapy
fluocinolone: PR, pharmaceutics
triamcinolone: DT, drug therapy
triamcinolone: PR, pharmaceutics
cyclosporin: DT, drug therapy
cyclosporin: PR, pharmaceutics
amphotericin B: DT, drug therapy
amphotericin B: PR, pharmaceutics
antibiotic agent: DT, drug therapy
antibiotic agent: PR, pharmaceutics
ciprofloxacin: DT, drug therapy
ciprofloxacin: PR, pharmaceutics
fluorouracil: DT, drug therapy
fluorouracil: PR, pharmaceutics
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

L139 ANSWER 28 OF 73 EMBASE

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, pharmaceutics
*drug carrier: TP, topical drug administration
polymer: PO, oral drug administration
polymer: PR, pharmaceutics
lipid: NA, intranasal drug administration
lipid: PO, oral drug administration
lipid: PR, pharmaceutics
polysaccharide: PR, pharmaceutics
DNA fragment: PR, pharmaceutics
chitosan: NA, intranasal drug administration
chitosan: PO, oral drug administration
chitosan: PR, pharmaceutics
chitosan: TP, topical drug administration
macrogol: NA, intranasal drug administration
macrogol: PO, oral drug administration
macrogol: PR, pharmaceutics
oil: NA, intranasal drug administration
oil: PO, oral drug administration
oil: PR, pharmaceutics
polyester: NA, intranasal drug administration
polyester: PO, oral drug administration
polyester: PR, pharmaceutics
polyester: TP, topical drug administration
polystyrene: PR, pharmaceutics
insulin: NA, intranasal drug administration
insulin: PO, oral drug administration
insulin: PR, pharmaceutics
insulin: PK, pharmacokinetics
poly(cyanoacrylate): TO, drug toxicity
poly(cyanoacrylate): PO, oral drug administration
poly(cyanoacrylate): PR, pharmaceutics
poly(cyanoacrylate): TP, topical drug administration
nanocapsule: PO, oral drug administration
nanocapsule: PR, pharmaceutics
copolymer: PO, oral drug administration
copolymer: PR, pharmaceutics
DNA vaccine: NA, intranasal drug administration
DNA vaccine: PR, pharmaceutics
tetanus toxin: NA, intranasal drug administration
tetanus toxin: PR, pharmaceutics
tetanus toxin: PD, pharmacology
indometacin: PR, pharmaceutics
indometacin: PK, pharmacokinetics
indometacin: TP, topical drug administration
cyclosporin A: IO, intraocular drug administration
cyclosporin A: PR, pharmaceutics
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

L139 ANSWER 29 OF 73 EMBASE

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, pharmaceutics
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

L139 ANSWER 30 OF 73 EMBASE

ACCESSION NUMBER: 2005405102 EMBASE Full-text

TITLE: The effects of LASIK on the ocular surface.

AUTHOR: Solomon R.; Donnenfeld E.D.; Perry H.D.

CORPORATE SOURCE: Dr. E.D. Donnenfeld, Ophthalmic Consultants of Long Island, Rockville Centre, 2000 North Village Avenue, New York, NY 11570, United States. eddoph@aol.com

SOURCE: Ocular Surface, (2004) Vol. 2, No. 1, pp. 34-44. .
Refs: 78
ISSN: 1542-0124

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 22 Sep 2005
Last Updated on STN: 22 Sep 2005

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

CONTROLLED TERM: Medical Descriptors:
*keratomileusis
***dry eye: CO, complication**
***dry eye: DI, diagnosis**
***dry eye: DT, drug therapy**
***dry eye: ET, etiology**
***dry eye: PC, prevention**
***cornea erosion: CO, complication**
***cornea erosion: ET, etiology**
***cornea erosion: SU, surgery**
***cornea erosion: TH, therapy**
tear film
denervation
postoperative care
treatment contraindication
surgical technique
risk factor
preoperative evaluation
lacrimal fluid
lacrimation
drug response
keratectomy
human
clinical trial
review
Drug Descriptors:
artificial tear: CM, drug comparison
artificial tear: DT, drug therapy
cyclosporin A: CT, clinical trial
cyclosporin A: CM, drug comparison
cyclosporin A: DT, drug therapy
cyclosporin A: TP, topical drug administration
doxycycline: PO, oral drug administration
methylprednisolone: DT, drug therapy
omega 3 fatty acid
icosapentaenoic acid
docosahexaenoic acid
linseed oil: DT, drug therapy
linseed oil: PO, oral drug administration
CAS REGISTRY NO.: **(cyclosporin A) 59865-13-3,** 63798-73-2; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (methylprednisolone) 6923-42-8, 83-43-2; (icosapentaenoic acid) 25378-27-2, 32839-30-8; (docosahexaenoic acid) 25167-62-8, 32839-18-2; (linseed oil) 8001-26-1
CHEMICAL NAME: **(1) Restasis**
COMPANY NAME: (1) Allergan

L139 ANSWER 31 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003476197 EMBASE Full-text
TITLE: The potential of chitosam in ocular drug delivery.
AUTHOR: Alonso M.J.; Sanchez A.
CORPORATE SOURCE: M.J. Alonso, Dept. of Pharm./Pharmaceut. Technol., Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain. ffmjalon@ucs.es
SOURCE: Journal of Pharmacy and Pharmacology, (2003) Vol. 55, No. 11, pp. 1451-1463. .
Refs: 76
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom

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

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

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

*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, pharmaceutics
idoxuridine: PD, pharmacology
polycaprolactone: CB, drug combination
polycaprolactone: PR, pharmaceutics
diazepam: CB, drug combination
diazepam: PR, pharmaceutics
diazepam: PD, pharmacology
polylysine: CB, drug combination
polylysine: PR, pharmaceutics
polylysine: PD, pharmacology

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

L139 ANSWER 32 OF 73 EMBASE

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:
***Sjoegren syndrome: DI, diagnosis**
***Sjoegren syndrome: DT, drug therapy**
***Sjoegren syndrome: EP, epidemiology**

***Sjoegren syndrome: ET, etiology**
***Sjoegren 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

L139 ANSWER 33 OF 73 EMBASE
ACCESSION NUMBER: 2002194457 EMBASE Full-text

TITLE: Management of dry eye syndrome.
AUTHOR: Lee G.A.
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, pharmaceutics
cyclosporin: DT, drug therapy
cyclosporin: PR, pharmaceutics
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 revital 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 revital 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

L139 ANSWER 34 OF 73 EMBASE

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, pharmaceutics
*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

L139 ANSWER 35 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
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)

L139 ANSWER 36 OF 73 EMBASE

ACCESSION NUMBER: 97232229 EMBASE Full-text

DOCUMENT NUMBER: 1997232229

TITLE: [**Cyclosporine** effect in corneal neovascularization].
EFECTO DE LA CICLOSPORINA SOBRE LA NEOVASCULARIZATION CORNEAL.

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

SOURCE: Revista Mexicana de Oftalmologia, (1997) Vol. 71, No. 2, pp. 41-43. .
Refs: 14
ISSN: 0187-4519 CODEN: RMOFEM

COUNTRY: Mexico

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

ABSTRACT: Human and animal investigations since the mid 1970's have demonstrated the effectiveness of **cyclosporine** (CsA) as an immunosuppresed 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/µl (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

L139 ANSWER 37 OF 73 EMBASE
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 Opthalmology, 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 cyclospolin 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**
***sjoegren syndrome: ET, etiology**
***sjoegren 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

sjoegren syndrome: TH, therapy

sjoegren syndrome: DT, drug therapy

spectacles

Drug Descriptors:

*artificial tear: DT, drug therapy

*artificial tear: PD, pharmacology

5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: DT, drug therapy

5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: PD, pharmacology

aldehyde reductase: EC, endogenous compound

alpha interferon: DT, drug therapy

alpha interferon: PD, pharmacology

arachis oil: PD, pharmacology

arachis oil: DT, drug therapy

arginylglycylaspartic acid: DT, drug therapy

arginylglycylaspartic acid: PD, pharmacology

cyclosporin a: PD, pharmacology

cyclosporin a: DT, drug therapy

dextran derivative: PD, pharmacology

dextran derivative: DT, drug therapy

epalrestat

epidermal growth factor: PD, pharmacology

epidermal growth factor: DT, drug therapy

fibronectin: EC, endogenous compound

hyaluronic acid: DT, drug therapy

hyaluronic acid: PD, pharmacology

hydroxypropylmethylcellulose: PD, pharmacology

hydroxypropylmethylcellulose: DT, drug therapy

retinoic acid: DT, drug therapy

retinoic acid: PD, pharmacology

retinol: PD, pharmacology

retinol: DT, drug therapy

tsukubaenolide: PD, pharmacology

tsukubaenolide: DT, drug therapy

visco tears

unclassified drug

CAS REGISTRY NO.: (5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione) 79714-31-1; (aldehyde reductase) 58591-34-7, 9023-11-4, 9028-31-3; (arachis oil) 8002-03-7, 8031-20-7; (arginylglycylaspartic acid) 99896-85-2; (**cyclosporin a**) **59865-13-3**, 63798-73-2; (epalrestat) 82159-09-9; (epidermal growth factor) 62229-50-9; (fibronectin) 86088-83-7; (hyaluronic acid) 31799-91-4, 9004-61-9, 9067-32-7; (hydroxypropylmethylcellulose) 9004-65-3; (retinoic acid) 302-79-4; (retinol) 68-26-8, 82445-97-4; (tsukubaenolide)

104987-11-3
CHEMICAL NAME: (1) Ct 112; (2) Kinedak; (3) Visco tears; Fk 506
COMPANY NAME: (1) Senju pharmaceutical (Japan); (2) Ono (Japan); (3) Alcon (United States)

L139 ANSWER 40 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
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, pharmaceutics
*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)

L139 ANSWER 41 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 92021561 EMBASE Full-text

DOCUMENT NUMBER: 1992021561

TITLE: [Sjoegren syndrome: Current therapy].
LA SINDROME DI SJOEGREN: ATTUALITA TERAPEUTICHE.

AUTHOR: Di Giacinto G.; Piergiacomi G.

CORPORATE SOURCE: Cattedra di Reumatologia, Universita degli Studi, Piazza Roma 22, 60128 Ancona, Italy

SOURCE: Clinica Terapeutica, (1991) Vol. 139, No. 3-4, pp. 81-92.
ISSN: 0009-9047 CODEN: CLTEA4

COUNTRY: Italy

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
011 Otorhinolaryngology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: Italian

SUMMARY LANGUAGE: English; Italian

ENTRY DATE: Entered STN: 20 Mar 1992

Last Updated on STN: 20 Mar 1992

CONTROLLED TERM: Medical Descriptors:

*disease severity

***sjoegren syndrome: DT, drug therapy**

***sjoegren syndrome: TH, therapy**

***sjoegren syndrome: SU, surgery**

anorexia: SI, side effect

chewing gum

diet

drug efficacy

human

intramuscular drug administration

intranasal drug administration

intravenous drug administration

kidney failure: SI, side effect

leukemia: SI, side effect

mouth ulcer: SI, side effect

nausea: SI, side effect

oral drug administration

rash: SI, side effect

rectal drug administration

review

topical drug administration

vomiting: SI, side effect

xerophthalmia

therapy

drug therapy

Drug Descriptors:

*antiinflammatory agent: AE, adverse drug reaction

*antiinflammatory agent: DT, drug therapy

*artificial tear: PR, pharmaceutics

*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, sphinogolipodoses, 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.

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

LAMBERT G; (RABI-I) RABINOVICH-GUILATT L
COUNTRY COUNT: 112
PATENT INFORMATION:

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

APPLICATION DETAILS:

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

PRIORITY APPLN. INFO: EP 2004-291684 20040702
INT. PATENT CLASSIF.:
MAIN: A61K009-00; A61K009-107; A61K048-00
SECONDARY: A61K031-4738; A61K031-4745; A61K031-70; A61K038-18; A61K038-19; A61K038-20; A61K038-21
BASIC ABSTRACT:
US2006002963 A UPAB: 20060201
NOVELTY - Treating **eye** diseases by injecting intraocularly or periocularly a composition (I) comprising an **emulsion** and optionally at least an active ingredient, is new.
ACTIVITY - Ophthalmological; Antiinflammatory; Cytostatic; Antidiabetic; Virucide.
MECHANISM OF ACTION - None given.
USE - (I) is useful for treating **eye** disease, and intraocular conditions such as intraocular inflammation, infection, cancerous growth, tumors, neo vessel growth originating from the retina and/or from the choroids, retinal edema, macular edema, diabetic retinopathy, retinopathy of prematurity, degenerative diseases of the retina (macular degeneration, retinal dystrophies), **retinal diseases** associated with glial proliferation, ocular conditions such as glaucoma, proliferative **vitreoretinopathy**, diabetic retinopathy, age-related macular degeneration, uveitis, cytomegalovirus retinitis, herpes simplex viral retinal dystrophies, age related macular degeneration (claimed).
The ability of (I) to treat ocular inflammation was assessed. The results showed that (I) exhibited a significant probability value of less than 0.05.
Dwg.0/2
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-A; B02-B; B02-C01; B02-C02; B02-D; B02-E; B02-M; B02-N; B02-P; B02-R; B02-T; B04-B01B; B04-B03C; B04-C01H; B04-C02E1; B04-E01; B04-E07A; B04-E07C;

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

TECH UPTX: 20060201

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

The **emulsion** further comprises additive such as osmotic pressure regulators, anti-oxidants, preservatives, dextrose, carriers, stabilizing agents, wetting agents, viscosity enhancersnalgesics, cell transport/mobility impending agents such as colchicines, vincristine, cytochalasin B and related compounds; carbonic anhydrase inhibitors such as acetazolamide, methazolamide, dichlorphenamide, diamox and neuroprotectants such as nimodipine and related compounds; antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalexin, oxytetracycline, chloramphenicol, rifampicin, ciprofloxacin, aminosides, gentamycin, erythromycin and penicillin, quinolone, ceftazidime, vancomycine imipeneme; antifungals such as amphotericin B, fluconazole, ketoconazole and miconazole; antibacterials such as sulfonamides, sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals such as idoxuridine, trifluorothymidine, trifluorouridine, acyclovir, ganciclovir, cidofovir, interferon, didanosine (DDI), zidovudine (AZT), foscamet, vidarabine, irbavirin, protease inhibitors and anti-cytomegalovirus agents; antiallergenics such as sodium cromoglycate, antazoline, methapyriline, chlorpheniramine, cetirizine, pyrilamine and prophenpyridamine; synthetic gluocorticoids 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 cyclooxegenase 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, florxymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, limustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostin, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard,

vinblastine, vincristine and vindesine; immunological drugs such as vaccines and immune stimulants; insulin, calcitonin, parathyroid hormone and peptide and vasopressin hypothalamus releasing factor; beta adrenergic blockers such as timolol, levobunolol and betaxolol; cytokines, interleukines and growth factors epidermal growth factor, fibroblast growth factor, platelet derived growth factor, transforming growth factor beta, ciliary neurotrophic growth factor, glial derived neurotrophic factor, nerve growth factor (NGF), erythropoietin (EPO), placenta growth factor (PLGF), brain nerve growth factor (BNGF), vascular endothelial growth factor (VEGF) and monoclonal antibodies directed against such growth factors; anti-inflammatories such as hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone and triamcinolone; decongestants chosen from the group comprising phenylephrine, naphazoline and 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-oxaazcyclotricosine-tetrone, also known as Tacrolimus), tumor necrosis factor, pentostatin, thymopentin, transforming factor beta-.sub.2, erythropoetin; 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 guars, 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 repellant, 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, phrilamine maleate, chlorpheniramine and tripelennamine, phenothiazines, promethazine hydrochloride, dimethindene maleate)), antiinflammatory agent (clobetasol proprionate, halobetasol proprionate, betamethasone diproprionate, 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, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone and trimethazone)), anticancer agent, retinoid (retinol, retinal, retinoic acid, etretinate, actiretin, isotretinoin, adapalene or tazarotene), an anti-wrinkle agent, sulfur-containing amino acids, thiol compounds, alpha hydroxy acids, lactic acid and lactic acid derivatives and salts, glycolic acid, glycolic acid derivatives and glycolic acid salts, beta-hydroxy acids, salicylic acid and salicylic acid salts and derivatives, phytic acid, lipoic acid, lysophosphatidic acid, skin peel agents, phenol, resorcinol, vitamin B3 compounds, niacinamide, nicotinic acid and nicotinic acid salts and esters, tocopheryl nicotinate, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide, retinoids, retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate and retinyl ascorbate, caffeine, theophilline, pentoxyphilline, dihydroxy acetone kojic acid, arbutin, nicotinic acid and nicotinic acid precursors, nicotinic acid salts, nicotinic acid derivatives, ascorbic acid, ascorbic acid salts or ascorbic acid derivatives, radical scavenger, herbal extract, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid and gallic acid alkyl esters, propyl gallate, uric acid, uric acid salts and alkyl esters, sorbic acid and sorbic acid salts, lipoic acid, N,N-diethylhydroxylamine, aminoguanidine, sulfhydryl compounds, glutathione, dihydroxy fumaric acid and fumaric acid salts, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin,

tea extract, grape skin/seed extract, melanin, rosemary extract, self-tanning agent, anti-acne active agent (further comprising retinoid, a keratolytically active agent and an 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, fluoroquinolnes, 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

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, tripelennamine, 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 diproprionate, betamethasone valerate, fluocinolone acetonide, halcinonide, betamethasone valerate, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide and/or hydrocortisone or oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, salicylate, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, 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, etretinate, actiretin, 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, theophilline, pentoxyphilline, 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 - Opthalmological.

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 cephlosporins. 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, carboxylmethyl 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), polycyanoacylate, 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, sterilzable, 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 Sjoegren 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, Sjoegren'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 glancoma, 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 tahn 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 prepns. (eyedrop, ointment) is composed of tetrandrine 0.001-2, synergistic drugs 0-5, excipient 93-99.999, metal ion complexing agent (disodium edetate) 0-5, isotonic regulator (sodium chloride) 0-10%, solubilizer (0.1-2 M HCl) 0.05-50 mL, thickening agent (hydroxymethyl cellulose) 0-5, cuticle lytic agent (borneol) 0-5, and antioxidant (sodium pyrosulfite) 0-5%, resp. Excipient in eyedrop is injection water; excipient in ointment is wool grease 0-20, paraffin oils 0-20, sodium Et cellulose 0.1-10, and addnl. vaseline to 1000 g. The synergistic drug is antimicrobial, such as erythrocin, kanamycin, gentamicin, amikacin, tobramycin, sisomycin, netilmicin, micronomicin, isepamicin, astromicin, etimicin, neomycin, spectinomycin, tetracycline, paromomycin, doxycycline, minocycline, sulfacetamide sodium, norfloxacin, ofloxacin, enoxacin, ciprofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, fleroxacin, moxifloxacin, rifampicin, metronidazole, tinidazole or cefoperazone; antiviral drugs, such as acyclovir, ganciclovir, valaciclovir or ribavirin; hormone drugs, such as dexamethasone phosphate, fluocinolone, beclometasone, etc.; vitamin, such as vitamin B1, vitamin B2, vitamin B6, vitamin B12 or vitamin C, niacinamide or folic acid; anti-inflammatory drug, such as indometacin, ibuprofen, meloxicam, piroxicam, diclofenac sodium, paracetamol or nimesulide; antianaphylactic drug, such as chlorphenamine, diphenhydramine, tripelennamine, 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 dipyridamole, 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.

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TITLE: Pharmaceutical compositions containing polyunsaturated fatty acid in combination with immunosuppressive