6

**NDA 21-023**

**Cyclosporine Ophthalmic Emulsion, 0.05%**

**Original NDA Filing**

**February 24, 1999**

**Volume 1 of 171**

File

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

March 3, 1999

Lori Gorski
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion, 0.05%
**NDA 21-023**

Dear Ms. Gorski,

In reference to a telephone conversation today with Dr. Su Tso, Chemistry Reviewer, please find the following information pertaining to NDA 21-023:

1. Allergan is requesting market approval for one concentration of cyclosporine ophthalmic emulsion, 0.05%.

2. Allergan confirms that the commercial pack consists of the unit dose vials in a polypropylene tray.

3. Allergan confirms that the 12-month stability data for the product in the commercial package will be available by mid to late April 1999.

4. Allergan confirms that all manufacturing and research facilities listed in NDA 21-023 are ready for the pre-approval inspection.

Thank you for your assistance with this project. Please contact me if you need any additional information at telephone (714) 246-4391 or fax (714) 246-4272.

Sincerely,

Elizabeth Bancroft
Director, Regulatory Affairs

cc: S. Tso, Chemistry Reviewer

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

File

**March 2, 1999**

Lori Gorski
Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Document Control Center, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-023
Cyclosporine Ophthalmic Emulsion. 0.05%

Dear Ms. Gorski –

Enclosed is one copy of the microbiological information from Section 4A, Chemistry, Manufacturing and Control (CMC) of NDA 21-023. These volumes are:

1) Volume 1 and 3 from the December 9, 1998 pre-submission of the CMC section containing information on the manufacturing process and test for sterility.

2) Volumes 2 through 11 from the February 24, 1999 original NDA submission containing information on the validation of the aseptic process.

The original pagination is retained. These data are contained in the white Microbiology review binders as requested.

If you have any questions concerning this or any other section of the NDA, please contact me at (714) 246-4391.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

EB/mkb

File

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

March 1, 1999

DESK COPY

Lori Gorski
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion, 0.05%
**NDA 21-023 – FIELD COPIES**

Dear Ms. Gorski,

Enclosed please find copies of the cover letters Allergan sent to the 2 Field Offices involved with the cyclosporine emulsion NDA. We sent an official Field Copy of the NDA to the LA District, to represent the corporate R&D offices in Irvine, CA, and a copy to the Dallas District to represent the manufacturing site in Waco, Texas.

If you have any questions, please let me know. Thank you for your assistance with this project. Please contact me if you need any additional information at telephone (714) 246-4391 or fax (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**March 1, 1999**

Tyler Thornburg
Director, US Activities Branch
Dallas District Office
Food and Drug Administration
3310 Live Oak
Dallas, TX 75204

RE: NDA 21-023
Original NDA – Field Copy of Chemistry, Manufacturing and Control Section

Dear Mr. Thornburg:

Enclosed are copies of the Chemistry, Manufacturing and Control (CMC) section for NDA 21-023. An archival and review copy of the enclosed binders were submitted to the FDA Maryland Office on the following dates:

| | |
|---|---|
| December 9, 1998 | Pre-submission of CMC |
| February 24, 1999 | Original NDA submission |

A certification that the enclosed volumes are an identical copy of the sections as they appear in the archival and review copy of the application is contained in Volume 1, page 1 147 of the February 24, 1999 submission.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

Enclosure (2 boxes)

EB/mkb

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**March 1, 1999**

Elaine Mesa
District Director
Irvine Office
19900 Mac Arthur Blvd.
Suite 300
Irvine, CA 92612-2445

RE: NDA 21-023
Original NDA – Field Copy of Chemistry, Manufacturing and Control Section

Dear Ms. Mesa:

Enclosed are copies of the Chemistry, Manufacturing and Control (CMC) section for NDA 21-023. An archival and review copy of the enclosed binders were submitted to the FDA Maryland Office on the following dates:

| | |
|---|---|
| December 9, 1998 | Pre-submission of CMC |
| February 24, 1999 | Original NDA submission |

A certification that the enclosed volumes are an identical copy of the sections as they appear in the archival and review copy of the application is contained in Volume 1, page 1 147 of the February 24, 1999 submission.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

Enclosure (2 boxes)

EB/mkb

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**March 1, 1999**

Tyler Thornburg
Director, US Activities Branch
Dallas District Office
Food and Drug Administration
3310 Live Oak
Dallas, TX 75204

RE: NDA 21-023
Original NDA – Field Copy of Chemistry, Manufacturing and Control Section

Dear Mr. Thornburg:

Enclosed are copies of the Chemistry, Manufacturing and Control (CMC) section for NDA 21-023. An archival and review copy of the enclosed binders were submitted to the FDA Maryland Office on the following dates:

| | |
|---|---|
| December 9, 1998 | Pre-submission of CMC |
| February 24, 1999 | Original NDA submission |

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Sincerely,

Elizabeth Bancroft
Director
Regulatory Affairs

Enclosure (2 boxes)

EB/mkb

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**March 1, 1999**

Elaine Mesa
District Director
Irvine Office
19900 Mac Arthur Blvd.
Suite 300
Irvine, CA 92612-2445

RE: NDA 21-023
Original NDA – Field Copy of Chemistry, Manufacturing and Control Section

Dear Ms. Mesa:

Enclosed are copies of the Chemistry, Manufacturing and Control (CMC) section for NDA 21-023. An archival and review copy of the enclosed binders were submitted to the FDA Maryland Office on the following dates:

| | |
|---|---|
| December 9, 1998 | Pre-submission of CMC |
| February 24, 1999 | Original NDA submission |

A certification that the enclosed volumes are an identical copy of the sections as they appear in the archival and review copy of the application is contained in Volume 1, page 1 147 of the February 24, 1999 submission.

Sincerely,

Elizabeth Bancroft
Director
Regulatory Affairs

Enclosure (2 boxes)

EB/mkb

File

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

# DESK COPY

February 24, 1999

Lori Gorski
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion, 0.05%
**NDA 21-023**

Dear Ms. Gorski,

As discussed, enclosed please find 20 copies of the first volume of NDA 21-023, Cyclosporine ophthalmic emulsion. The Archival and Review copies of the entire NDA were shipped to the Central Document Room on Wednesday, February 24, 1999.

Also enclosed please find one copy of the electronic version (.pdf files) of the NDA on 4 CD Rom disks. Please note that the disks should be copied onto a network or a hard drive so that all files can be accessed. The files cannot be accessed on multiple CDs by pointing from one to another. If you require additional copies of the CD Rom disks or additional instructions on how to navigate through the files, please let me know. The Word versions of the files will be sent under separate cover as soon as they are compiled.

Thank you for your assistance with this project. Please contact me if you need any additional information at telephone (714) 246-4391 or fax (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

file

February 17, 1999

U. S. Food and Drug Administration
C/O Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

**NDA 21-023**
**Cyclosporine ophthalmic emulsion**
**User Fee Number 3632 Application Fee Payment**

Dear Sir or Madam:

In accordance with your Establishment of Prescription Drug User Fee Rates for Fiscal Year 1999, enclosed please find Allergan's check number 103765, dated February 1, 1999, in the amount of $272,282. This represents full payment for our Cyclosporine ophthalmic emulsion application, which requires clinical data.

If you have any questions or concerns, please contact me at (714) 246-4391.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director, Regulatory Affairs

EB/dmo
Enclosure: Check Number 103765

**ALLERGAN**
Irvine, California 92623

Account with Vendor 1000003970
Account at Vendor

Check Number 103765
Document Number 84002545
Date 02/01/1999

FOOD AND DRUG ADMINISTRATION
C/O MELLON BANK
PO box 360909
PITTSBURGH PA 15251-6909

| Voucher Number | Purchase Order | Invoice Number | Invoice Date | Gross Amount | Discount | Net Amount |
|---|---|---|---|---|---|---|
| 31502821 | | CKRQ012199<br>USER FEE NUMBER 3632 | 01/21/1999 | 272,282.00 | 0.00 | 272,282.00 |
| | | | Total | 272,282.00 | 0.00 | 272,282.00 |

DO NOT CASH THIS CHECK UNLESS YOU CAN SEE THE WORD "SAFE" IN THE BACKGROUND
HOLD AT AN ANGLE TOWARDS OR AWAY FROM A LIGHT TO VERIFY SAFETY FEATURES FRONT & BACK

WACHOVIA BANK OF NORTH CAROLINA, N.A.
WINSTON-SALEM, NORTH CAROLINA

66-763
531

**ALLERGAN**
Irvine, California 92623

Check Number
103765
THIS NUMBER BLEEDS THRU TO BACK

USER FEE NUMBER 3632

Date
02/01/1999

Net Amount
$ *******272,282.00*

PAY

*** TWO HUNDRED SEVENTY-TWO THOUSAND TWO HUNDRED EIGHTY-TWO USD***

TO THE ORDER OF
FOOD AND DRUG ADMINISTRATION
C/O MELLON BANK
PO box 360909
PITTSBURGH PA 15251-6909

⑈103765⑈ ⑆053107633⑆018739 006917⑈

**ALLERGAN** CHECK REQUEST

**INVOICE # CKRQ**
ACCOUNTS PAYABLE USE ONLY

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- ☐ AGN, INC - 0010
- ☐ VPLP - 0040
- ☐ WACO - 0050
- ☐ SURGICAL - 0110
- ☐ AGN SALES - 0120
- ☐ OMS - 0150
- ☒ AGN SERVICES - 0170
- ☐ AGN AMERICA
- ☐ AMO (PUERTO RICO)
- ☐ CANADA
- ☐ HATO REY, PUERTO RICO
- ☐ OTHER _____

MAKE CHECK PAYABLE TO:
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**1/21/99**

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**Mellon Bank (FDA 360909)**
**Three Mellon Bank Center, 27th Floor**

CITY/STATE/PROVINCE/COUNTRY: ZIPCODE:
**Pittsburgh, PA 15259-0001**

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- -

**OR**
**Tax I.D. #**
-

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U.S. $ ☐
_____ OTHER ☐

EXPLANATION:
**User Fee for Cyclosporine NDA submission, User Fee Number 3632**

## SHOULD THIS BE ON THE PURCHASING CARD?

THE SHADED FIELDS ARE THE MINIMUM FIELDS REQUIRED.

| | PC | CO. CODE | ACCOUNT | COST CENTER | PROD | SC | AMOUNT |
|---|---|---|---|---|---|---|---|
| | | | 5913001 | 20030120 1081 | | | $272,282.00 |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| *(FOR CANADIAN USE ONLY)* | | | | | | | |
| QST | 001 | 1 | 2120 | 00 | 000 | 51 | |
| GST | 001 | 1 | 2120 | 00 | 000 | 09 | |
| CHECK TOTAL | | | | | | | $272,282.00 |

PREPARED BY *(PLEASE PRINT)*:
**Elizabeth Bancroft**

APPROVED SIGNATURE MUST APPEAR ON "AUTHORIZED SIGNATURE LIST"

APPROVED BY *(PLEASE PRINT)*: **Peter Kresel, Sr. VP**
*(SIGNATURE)*: Peter Kresel
YOUR $ LIMIT: **$1 million**
DATE: 1/26/99

**NOTE: INSTRUCTIONS TO PREPARER**
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**2. ATTACH SUPPORTING DOCUMENTATION. WITHOUT DOCUMENTATION, THIS FORM WILL BE RETURNED.**
**3. PLEASE DO NOT USE THIS FORM FOR THE FOLLOWING:**
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**4-Feb-99**

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| NAME: | EXT.: | MAIL CODE: |
|---|---|---|
| **Elizabeth Bancroft** | **4391** | **LS-1F** |

C.C.:

APG 360 REV. 10/97 PA WHITE - ACOUNTS PAYABLE YELLOW - REQUESTER

63 FR 70777 Tuesday, December 22, 1998
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Establishment of Prescription Drug User Fee Rates for Fiscal Year 1999

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the rates for prescription drug user fees for fiscal year (FY) 1999. The Prescription Drug User Fee Act of 1992 (the PDUFA), as amended by the Food and Drug Administration Modernization Act of 1997 (the FDAMA), authorizes FDA to collect user fees for certain applications for approval of drug and biological products, on establishments where the products are made, and on such products. Fees for applications for FY 1999 were set by the FDAMA, subject to adjustment for inflation. Total application fee revenues fluctuate with the number of fee-paying applications FDA receives. Fees for establishments and products are calculated so that total revenues from each category will approximate FDA's estimate of the revenues to be derived from applications.

FOR FURTHER INFORMATION CONTACT: Michael E. Roosevelt, Office of Financial Management (HFA-120), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-5088.

SUPPLEMENTARY INFORMATION:

## I. Background

The PDUFA (Pub. L. 102-571), as amended by the FDAMA (Pub. L. 105- 115), establishes three different kinds of user fees. Fees are assessed on: (1) Certain types of applications and supplements for approval of drug and biological products, (2) certain establishments where such products are made, and (3) certain products (21 U.S.C. 379h(a)). When certain conditions are met, FDA may waive or reduce fees (21 U.S.C. 379h(d)).

For 1998 through 2002, under the amendments enacted in the FDAMA, the application fee rates are set in the statute, but are to be adjusted annually for cumulative inflation since 1997. Total application fee revenues are structured to increase or decrease each year as the number of fee-paying applications submitted to FDA increases or decreases (workload adjustment).

For 1998 through 2002, FDA is required to set fee rates for establishment and product categories each year, so that the total fee revenue from each of these two categories are projected to be equal to the total revenue FDA expects to collect from application fees that year. This procedure continues the arrangement under which one-third of the total user fee revenue is projected to come from each of the three types of fees--application fees, establishment fees, and product fees.

This notice establishes fee rates for FY 1999 for application, establishment, and product fees. These fees are retroactive to October 1, 1998, and will remain in effect through September 30, 1999. For fees already paid on applications and supplements submitted on or after October 1, 1998, FDA will bill applicants for the difference between fees paid and fees due under the new fee schedule. For applications and supplements submitted after December 31, 1998, the new fee schedule must be used. Invoices for establishment and product fees for FY 1999 will be issued in December 1999, using the new fee schedules.

## II. Inflation and Workload Adjustment Process

The PDUFA, as amended by the FDAMA, provides that fee rates for each FY shall be adjusted by notice in the Federal Register. The adjustment must reflect the greater of: (1) The total percentage change that occurred during the preceding FY in the Consumer Price Index (CPI), or (2) the total percentage pay change for that FY for Federal employees stationed in the Washington, DC metropolitan area. The FDAMA provides for this annual adjustment to be cumulative and compounded annually after 1997 (see 21 U.S.C. 379h(c)(1)).

The FDAMA also structures the total application fee revenue to increase or decrease each year as the number of fee-paying applications submitted to FDA increases or decreases. This provision allows revenues to rise or fall as this portion of FDA's workload rises or falls. To implement this provision each year, FDA will estimate the number of fee-paying applications it anticipates receiving. The number of applications estimated will then be multiplied by the inflation-adjusted statutory application fee. This calculation will produce the FDA estimate of total application fee revenues to be received.

The PDUFA also provides that FDA shall adjust the rates for establishment and product fees so that the total revenues from each of these categories is projected to equal the revenues FDA expects to collect from application fees that year. The FDAMA provides that the new fee rates based on these calculations be adjusted within 60 days after the end of each FY (21 U.S.C. 379h(c)(2)).

## III. Inflation Adjustment and Estimate of Total Application Fee Revenue

The FDAMA provides that the application fee rates set out in the statute be adjusted each year for cumulative inflation since 1997. It also provides for total application fee revenues to increase or decrease based on increases or decreases in the number of fee-paying applications submitted.

### A. Inflation Adjustment to Application Fees

Application fees are assessed at different rates for qualifying applications depending on whether the applications require clinical data on safety or effectiveness (other than bioavailability or bioequivalence studies) (21 U.S.C. 379h(a)(1)(A) and (b)). Applications that require clinical data are subject to the full application fee. Applications that do not require clinical data and supplements that require clinical data are assessed one-half the fee of applications that require clinical data. If FDA refuses to file an application or supplement, 75 percent of the application fee is refunded to the applicant (21 U.S.C. 379h(a)(1)(D)).

The application fees described previously are set out in the FDAMA for 1999 ($256,338 for applications requiring clinical data, and $128,169 for applications not requiring clinical data or supplements requiring clinical data) (21 U.S.C. 379h(b)(1)), but must be adjusted for cumulative inflation since 1997. That adjustment each year is to be the greater of: (1) The total percentage change that occurred during the preceding FY in the CPI (all items; U.S. city average); or (2) the total percentage pay change for that FY for Federal employees, as adjusted for any locality-based payment applicable to employees stationed in the District of Columbia. The FDAMA provides for this annual adjustment to be cumulative and compounded annually after 1997 (see 21 U.S.C. 379h(c)).

The adjustment for FY 1998 was 2.45 percent (62 FR 64849, December 9, 1997). This was the greater of the CPI increase for FY 1997 (2.15 percent) and the increase in applicable Federal salaries (2.45 percent).

The adjustment for FY 1999 is 3.68 percent. This is the greater of the CPI increase for FY 1998 (1.49 percent) and the increase in applicable Federal salaries (3.68 percent).

Compounding these amounts (1.0245 times 1.0368) yields a total compounded inflation of 6.22 percent for FY 1999. The adjusted application fee rates are computed by applying the inflation percentage for FY 1999 (106.22 percent) to the FY 1999 statutory application fee rates stated previously. For FY 1999 the adjusted application fee rates are $272,282 for applications requiring clinical data, and $136,141 for applications not requiring clinical data or supplements requiring clinical data. These amounts must be submitted with all applications during FY 1999.

B. Estimate of Total Application Fee Revenue

Total application fee revenues for 1999 will be determined by the number of fee-paying applications FDA receives in FY 1999 (from October 1, 1998, through September 30, 1999) multiplied by the fee rates calculated in the preceding paragraph. Before fees can be set for establishment and product fee categories, each of which are projected to be equal to total revenues FDA collects from application fees, FDA must first estimate its total 1999 application fee revenues. To do this FDA has traditionally calculated the number of full application fees FDA received in the preceding fiscal year, made an allowance for waivers and exemptions, and used that figure as a basis for estimating the next year's application volume.

For FY 1998, FDA received and filed 101 human drug applications that require clinical data for approval, 23 that did not require clinical data for approval, and 93 supplements to human drug applications that require clinical data for approval. Because applications that do not require clinical data and supplements that require clinical data are assessed only one-half the full fee, the equivalent number of these applications subject to the full fee is determined by summing these categories and dividing by 2. This amount is then added to the number of applications that require clinical data to arrive at the equivalent number of applications that may be subject to full application fees.

In addition, as of September 30, 1998, FDA assessed fees for three applications that required clinical data, one application that did not require clinical data, and one supplement, all of which were refused filing or withdrawn before filing. After refunds, the full application paid one-fourth the full application fee and is counted as one-fourth of an application, and the application that did not require clinical data and the supplement each paid one-eighth of the full application fee and are each counted as one-eighth of an application.

Using this methodology, the approximate equivalent number of applications that required clinical data and were subject to fees in FY 1998 was 160, before any exemptions, waivers or reductions. Under the FDAMA, FDA may waive fees for certain small businesses submitting their first application and certain orphan products are exempted from application fees. In addition, the FDAMA excludes from fees bulk biological products that are further manufactured, and provides exceptions for certain supplements for pediatric indications. In FY 1998 waivers or exemptions applied to 41.5 equivalents of full applications. Therefore, based solely on 1998 data, FDA estimates that approximately 118.5 (160 minus 41.5) equivalent applications that require clinical data will qualify for fees in FY 1999, after allowing for exemptions, waivers, or reductions.

This estimate based on the data from 1998 alone predicts a substantial drop in applications, and represents a substantial departure from FDA experience over the past 5 years. Over that period the estimated number of fee-paying applications increased fairly consistently at a rate of about 7 percent each year, as set out in Table 1 of this document.

Table 1.

| Year | Estimated Number of Fee-Paying Full Application Equivalents |
|---|---|
| 1993 | 116 |
| 1994 | 124 |
| 1995 | 131 |
| 1996 | 141 |
| 1997 | 169 |
| 1998 | 118.5 |

Since the volume of fee-paying applications FDA received in 1998 represents such a substantial departure from the trend experienced over the previous 5 years, and since sharp changes produce disruptive volatility in both fees and revenues, FDA reexamined the process to be used in estimating the next year's application volume. FDA considered several different approaches (continuation of current method, using

a 2- or 3-year rolling average, and linear regression) and chose the linear regression projection method as the best alternative for this estimate.

Linear regression is well suited to situations like this where there are several years of historical data, the potential exists for shifts from year-to-year, and there is no obvious causative rationale to reasonably predict the year-to-year fluctuations. It also provides a damping effect on year-to-year fee and revenue fluctuations and allows for more stability in both fee levels paid by industry and in agency resource planning. Under this approach, the analysis takes into account the number of fee-paying PDUFA submissions each year since PDUFA began in 1993, adjusts those numbers conservatively to reflect additional exemptions/waivers that would have been granted between 1993 and 1997 if the current law governing exemptions and waivers had been in effect then, and fits the best line to those data points. The extension of that line to the next year estimates the number of submissions for that year. Beginning now for FY 1999, FDA will make this annual estimate based on a linear regression analysis of data on all fee-paying full application equivalent submissions from 1993 through the latest year (1998 in this case).

This will mean that our estimated number of applications will be higher in 1998 than it would have been under our previous estimating method. It will also mean that in future years, if there is a sudden rise in application volume, the regression analysis process will dampen the effect of such year-to-year increases as well. We believe that this is a fair and reasonable approach, and that it will insulate fees and revenues from significant fluctuations that may occur in any single year.

Using this approach, a linear regression line based on the adjusted number of fee-paying full application equivalent submissions since 1993 projects the receipt of 150 fee-paying full application equivalent submissions in 1999, as reflected in Table 2 and the graphic of this document.

Table 2.

| Year | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 |
|---|---|---|---|---|---|---|---|
| Adjusted Fee-Paying Full Application Equivalents | 101.0 | 108.9 | 112.5 | 136.3 | 161.5 | 118.5 | |
| Regression Line | 103.9 | 111.6 | 119.3 | 127.0 | 134.6 | 142.3 | 150.0 |

BILLING CODE 4160-01-F

[GRAPHIC] [TIFF OMITTED] TN22DE98.022

BILLING CODE 4160-01-C

The total FY 1999 application fee revenue is estimated by multiplying the adjusted application fee rate ($272,282) by the equivalent number of applications projected to qualify for fees in FY 1999 (150), for a total estimated application fee revenue in 1999 of $40,842,300. This is the amount of revenue that FDA is also expected to derive both from establishment fees and from product fees.

IV. Fee Calculations for Establishment and Product Fees

A. Establishment Fees

At the beginning of FY 1998 the establishment fee was based on an estimate of 275 establishments subject to fees. By the end of FY 1998, 343 establishments qualified for and were billed for establishment fees, before all decisions on requests for waivers or reductions were made. We estimate that a total of 25 establishment fee waivers will be granted in 1998, for a net of 318 fee-paying

establishments. In FY 1999 fees will be based on an estimate of 318 establishments paying fees after taking waivers into account. The fee per establishment is determined by dividing the adjusted total fee revenue to be derived from establishments ($40,842,300), by the estimated 318 establishments, for an establishment fee rate for FY 1999 of $128,435 (rounded to the nearest dollar).

B. Product Fees

At the beginning of FY 1998 the product fee was based on an estimate that 2,100 products would be subject to product fees. By the end of FY 1998, 2,279 products qualified and were billed for product fees before all decisions on requests for waivers or reductions were made. Assuming that there will be about 55 waivers granted, FDA estimates that 2,224 products will qualify for product fees in FY 1999, after allowing for waivers and exemptions. Accordingly, the FY 1999 product fee rate is determined by dividing the adjusted total fee revenue to be derived from product fees ($40,842,300) by the estimated 2,224 products for a product fee rate of $18,364 (rounded to the nearest dollar).

V. Adjusted Fee Schedules for FY 1999

The fee rates for FY 1999 are set out in Table 3 of this document.

Table 3.

Fee Category Fee Rates For FY 1999

Applications

| | |
|---|---|
| Requiring clinical data | $272,282 |
| Not requiring clinical data | $136,141 |
| Supplements requiring clinical data | $136,141 |
| Establishments | $128,435 |
| Products | $18,364 |

VI. Implementation of Adjusted Fee Schedule

A. Application Fees

Any application or supplement subject to fees under the PDUFA that is submitted after December 31, 1998, must be accompanied by the appropriate application fee established in the new fee schedule. Payment must be made in United States currency by check, bank draft, or U.S. postal money order payable to the order of the U.S. Food and Drug Administration. Please include the user fee ID number on your check.

Your check can be mailed to: Food and Drug Administration, P.O. Box 360909, Pittsburgh, PA 15251-6909.

If checks are to be sent by a courier that requests a street address, they can be sent to: Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001. (Note: This Mellon Bank Address is for courier delivery only.) Please make sure that the FDA P.O. Box number (P.O. Box 360909) is on the enclosed check.

FDA will bill applicants who submitted application fees between October 1, 1998, and December 31, 1998, based on the adjusted rate schedule.

B. Establishment and Product Fees

By December 31, 1998, FDA will issue invoices for establishments and product fees for FY 1999 under the new fee schedules. Payment will be due by January 31, 1999. FDA will issue invoices in October 1999 for any products and establishments subject to fees for FY 1999 that qualify for fees after the December 1998 billing.

**WORLDWIDE REGULATORY AFFAIRS**
**APPROVAL SHEET**

| REVIEWER | SIGNATURE | DATE | DATE |
|---|---|---|---|
| **Elizabeth Bancroft**<br>**RA Director** | | 1/25/99 | |
| **Peter Kresel**<br>**Sr. VP Global RegAff** | | 2/4/99 | |
| **Bob Koda**<br>**RA Consultant** | N/A | | |

| | | |
|---|---|---|
| **PRODUCT:** | **Cyclosporine Ophthalmic Emulsion** | |
| **PROJECT:** | **NDA Sections 1 through 3** | |
| **COUNTRY:** | **USA** | |
| **ANALYST:** | **Mari Bradford (X4392)** | **DATE ROUTED:** |
| **DATE MAILED:** | | |

**Volume 1 Table of Contents** **Vol. Page**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations 314 & 601)*

*Form Approved: OMB No. 0910-0338*
*Expiration Date: April 30, 2000*
*See OMB Statement on last page.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

**APPLICANT INFORMATION**

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Allergan, Inc. | 2/24/99 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| 800/347-4500 | 714/246-4272 |

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-023

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Cyclosporine USP | |
| **CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME** *(if any)* | **CODE NAME** *(if any)* |
| Not applicable | AGN 192371 |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Ophthalmic Emulsion | 0.05% | Topical - ophthalmic |

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate to severe keratoconjunctivitis sicca to restore and maintain normal tear secretion and ocular surface integrity

**APPLICATION INFORMATION**

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Not applicable Holder of Approved Application

TYPE OF SUBMISSION (check one)
☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Request for marketing approval

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 171 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

**ESTABLISHMENT INFORMATION**

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to attachment

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

IND 32,133 Allergan, Inc.,
DMF 1572 Chevron Chemical Company
NDA 50-073 & 50-074 Novartis Pharmaceutical Corporation
DMF 11086 Allergan, Inc.

**FORM FDA 356h (4/97)**

| This application contains the following items: (Check all that apply) | |
|---|---|
| X | 1. Index |
| X | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| X | 3. Summary (21 CFR 314.50 (c)) |
| X | 4. Chemistry section |
| X | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| X | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| X | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| X | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| X | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| X | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| X | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| X | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| X | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| X | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| X | 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| X | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| X | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| X | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| X | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| X | 18. User Fee Cover Sheet (Form FDA 3397) |
| | 19. OTHER (Specify) |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in applications in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Elizabeth Bancroft | Elizabeth Bancroft, Director, Regulatory Affairs | 2/24/99 |

| ADDRESS (*Street, City State, and ZIP Code*) | Telephone Number |
|---|---|
| 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 | (714) 246-4391 |

**Public reporting burden for this collection of information** is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201
Please **DO NOT RETURN** this form to this address.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**FORM FDA 356h (4/97)**

**Continuation Sheet for**

**Cyclosporine Ophthalmic Emulsion, 0.05% and 0.1%**
**NDA 21-023**

**ESTABLISHMENT INFORMATION FOR DRUG SUBSTANCE**

| Drug Substance | Manufacturing, Packing and Control Site | DMF No. | Telephone Number |
|---|---|---|---|
| Cyclosporin A | Novartis Pharma AG*<br>Lichstrasse 35<br>CH-4002 Basle<br>SWITZERLAND<br>(*Formerly Sandoz Pharma Ltd.)<br><br>and<br><br>Novartis Ringaskiddy Ltd.<br>Ringaskiddy<br>County Cork<br>IRELAND | NDA 50-073 &<br>NDA 50-074 | 41-61-324-7127<br>Contact Person:<br>Dr. Martin Hohermuth,<br>Drug Registration and<br>Regulatory Affairs<br><br>353-21-862-259<br>Contact Person:<br>Ms. Mary Bourke |

**ESTABLISHMENT INFORMATION FOR DRUG PRODUCT**

**Drug Product:** Cyclosporine Ophthalmic Emulsion, 0.05% and 0.1%

**Application Number:** NDA 21-023

| Responsibility | License No. | Contact |
|---|---|---|
| **Manufacturing, Packing and Control Site:** | | |
| Allergan, Inc.<br>8301 Mars Drive<br>Waco, TX 76712<br>USA | CFN= 1643525 | Elizabeth Bancroft, Director<br>Regulatory Affairs<br>Allergan, Inc.<br>(714) 246-4391 |
| **Site for stability testing of drug product:** | | |
| Allergan Pharmaceuticals (Ireland) Ltd., Inc.<br>Castlebar Road<br>Westport<br>County Mayo<br>IRELAND | CFN=FCE 1018 | Elizabeth Bancroft, Director<br>Regulatory Affairs<br>Allergan, Inc.<br>(714) 246-4391 |

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**

Form Approved: OMB No. 0910-0297
Expiration Date: 2/28/97

# USER FEE COVER SHEET



***See Instructions on Reverse Before Completing This Form.***

**1. APPLICANT'S NAME AND ADDRESS**

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

**2. USER FEE BILLING NAME, ADDRESS AND CONTACT**

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Contact: Elizabeth Bancroft

**3. TELEPHONE NUMBER (Include Area Code)**
800-347-4500

**4. PRODUCT NAME** Cyclosporine Ophthalmic Emulsion, 0.05%

**5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?** ☒ YES ☐ NO

**IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM**

**6. USER FEE I.D. NUMBER**
3632

**7. LICENSE NUMBER/NDA NUMBER**
N021023

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ **A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92**

☐ **THE APPLICATION IS SUBMITTED UNDER 505(b)(2)** *(See reverse before checking box.)*

☐ **AN INSULIN PRODUCT SUBMITTED UNDER 506**

FOR BIOLOGICAL PRODUCTS ONLY

☐ **WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION**

☐ **A CRUDE ALLERGENIC EXTRACT PRODUCT**

☐ **BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92**

☐ **AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT**

9.a. HAS THIS APPLICATION QUALIFIED FOR A **SMALL BUSINESS EXCEPTION?** ☐ YES ☒ NO
***(See reverse if answered YES)***

b. HAS A **WAIVER** OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
***(See reverse if answered YES)***

***This completed form must be signed and accompany each new drug or biologic product, original or supplement.***

| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| Elizabeth Bancroft | Elizabeth Bancroft<br>Director, Regulatory Affairs | 2/24/99 |

FORM FDA 3397 (11/96)

## INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
## FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplement submitted to the Agency on or after January 1, 1994. The Prescription Drug User Fee Act of 1992, Public Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing of the submission.

**ITEM NOS.** **INSTRUCTIONS**

1-3 Self-explanatory

4 **PRODUCT NAME** - Include the generic name and the trade name, as applicable.

5 If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug User Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.

6 **USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME.** FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT, please supply the following identifying information:

**FOR DRUG PRODUCTS** - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269.

**FOR BIOLOGIC PRODUCTS** - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906.

**EXAMPLE:** For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.

7. **LICENSE NUMBER/NDA NUMBER**

**FOR BIOLOGIC PRODUCTS** - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

**FOR DRUG PRODUCTS** - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035.

**EXAMPLE**: For NDA99999, the number would be: N099999.

8. **EXCLUSIONS** - Check the appropriate box if this application is NOT covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act.

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are **NOT** for a new molecular entity which is an active ingredient (including any salt of ester of an active ingredient); or **NOT** a new indication for use.

9. **WAIVER** - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.

BACK

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**February 24, 1999**

Center for Drug Evaluation and Research
Central Document Control
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20857

RE: NDA 21-023; Cyclosporine Ophthalmic Emulsion, 0.05%
Original NDA Filing

To Whom It May Concern:

Allergan hereby submits both an archival and review copy of the NDA for Cyclosporine ophthalmic emulsion. A pre-submission of the Chemistry, Manufacturing and Controls section of this NDA was filed on December 9, 1998. On February 17, 1999 the Sponsor mailed in the required user fee for this application under User Fee I.D. number 3632.

The subject of NDA 21-023 is Cyclosporine ophthalmic emulsion, 0.05% which is indicated for the treatment of moderate to severe keratoconjunctivitis sicca (KCS) to restore and maintain normal tear secretion and ocular surface integrity while providing relief of symptoms associated with dry-eye when dosing twice daily. The applicant hereby requests priority review status for this product since it is the first therapeutic product for the treatment of KCS, and therefore, would provide a significant improvement in the safe and efficacious treatment of the disease.

The active pharmaceutical ingredient (API), Cyclosporine USP, is manufactured by Novartis Pharma AG, located in Basel, Switzerland and Ringaskiddy, County Cork, Ireland. The chemistry, manufacturing and control of the API is reported by Novartis in approved NDA 50-073 and NDA 50-074. A letter authorizing FDA to review the data in these NDAs on behalf of Allergan is included in the application.

The finished drug product is a sterile preservative-free, oil-in-water emulsion containing 0.05% (ww) cyclosporine USP. The inactive ingredients are castor oil PhEur, polysorbate 80 NF, carbomer 1342 NF, glycerin USP, sodium hydroxide USP and purified water USP. The formulation has a target pH of 7.4. The primary packaging is a single-use unit dose vial (0.4 mL fill volume in 0.9 mL fill capacity) manufactured as part of a form-fill-seal operation from virgin low-density polyethylene resin. A 24 month expiration dating is proposed for Cyclosporine emulsion, 0.05%, in the proposed marketing configuration when stored at USP controlled room temperature.

Topical cyclosporine emulsion is therapeutic through three concurrent mechanisms: it is an immunomodulatory agent, an anti-inflammatory agent, and an anti-apoptotic. A

number of nonclinical safety studies were conducted in animals to support the ocular and systemic safety after ocular dosing of cyclosporine. In albino rabbits and beagle dogs topical administration produced no local or systemic toxic effects. There were no changes in the kidney, which is the target organ of systemic toxicity with cyclosporine at high doses, nor were there any liver changes. Likewise, no changes were observed in any organ, tissue, or in the peripheral blood. No neurotoxicity was observed and all ocular tissues were normal and without ocular infections.

Nonclinical pharmacokinetic studies established that cyclosporine concentrations during ophthalmic treatment are high in ocular target tissues and extremely low in blood which is consistent with ocular efficacy and further indicative of systemic safety. Maximal concentration obtained from rabbit and dog studies indicate that the great majority of drug contained in ocular tissues after ophthalmic administration resides in the outer layers of the eye, and that little penetrates to the interior. High concentrations and long half-lives in ocular surface tissues suggest that these tissues act as a reservoir for cyclosporine, sequestering cyclosporine and releasing it slowly over prolonged periods. Half-lives in conjunctiva, cornea and sclera after multiple ophthalmic doses to albino rabbits ranged from 32 to 52 hours. Half-lives in beagle dogs after multiple ophthalmic doses were also longer than 24 hours.

Blood cyclosporin A concentrations in humans were measured using a specific high-pressure liquid chromatography/mass spectrometry assay. Blood concentrations of cyclosporin A in all samples collected, after twice daily topical administration of cyclosporine emulsion, 0.05%, for up to 12 months, were below the quantitation limit of 0.1 ng/mL. These levels are more than 6550 times lower than those measured during systemic cyclosporine treatment for non-life-threatening indications. There was no detectable drug accumulation in blood during 12 months of treatment with Cyclosporine ophthalmic emulsion.

This NDA contains the results of two pivotal studies and one dose ranging study to support the safety and efficacy of Cyclosporine ophthalmic emulsion, 0.05% for the treatment of moderate to severe keratoconjunctivitis sicca. These studies achieved clinically and statistically significant results versus vehicle for the individual parameters corneal staining, blurred vision, categorized Schirmer with anesthesia, and reduction in artificial tear use. Improvement from baseline with Cyclosporine emulsion was seen in virtually all efficacy parameters. In addition, no bacterial or fungal ocular infections were reported following administration. Results of additional tests performed in the clinical trials following 6 months of treatment showed reduction of inflammation and immune reactivity underlying KCS, and improved ocular surface health and tear film in dry-eye patients with or without Sjögren's syndrome.

On December 9, 1998 Allergan filed a pre-submission of the Chemistry, Manufacturing and Controls section of NDA 21-023. At that time the Sponsor made a commitment to supplement the filing with the following items: aseptic process validation report

(Appendix 4A.5.3.2, original page 1 073) and completion of the commercial-scale batch results table (Section 4A.3.4.7, original page 1 040). These items are available in the current NDA filing Section 4 which also contains replacement pages for various subsections of 4A, clarification to items requested during a February 8, 1999 telephone call from Dr. Tso, FDA Reviewing Chemist, a statement and tabular listing of samples (Section 4B), and the methods validation package (Section 4C).

Allergan has manufactured three commercial size batches of the drug product at its manufacturing facility located in Waco, Texas. We are ready for a pre-approval inspection of the manufacturing site.

On January 12, 1998 the Sponsor requested that the Agency comment on the following proposed trade name for the product: RESTASIS™ (cyclosporine ophthalmic emulsion, 0.05%). We are hereby requesting reconfirmation that the proposed trade name is acceptable.

Allergan concludes that all available clinical, human pharmacokinetics and preclinical studies performed on the drug product indicate that it is safe and effective for its intended use. This product is also the first therapeutic product for the treatment of keratoconjunctivitis sicca. Therefore, Allergan is requesting that it receive priority review.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

EB/mkb

1.1 MASTER INDEX



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## 1.2 PRIOR RELATED SUBMISSIONS

## 1.2 LIST OF PRIOR RELATED SUBMISSIONS

Meetings and discussions between the Agency and Allergan are outlined below. A copy of each document is enclosed.

| Submission Date | IND Serial Number | Subject/Interaction |
|---|---|---|
| 08/26/96 | 066 | Allergan letter of understanding following the end-of-Phase 2 meeting of 6/4/96 |
| 12/09/96 | 068 | Allergan letter of understanding following the second end-of-Phase 2 meeting of 10/24/96 |
| 05/21/97 | 079 | Allergan letter of understanding following the CMC meeting of 4/24/97 |
| 01/12/98 | 087 | Allergan letter requesting Agency comments on tradename (RESTASIS) |
| 06/25/98 | N/A | 5/29/98 telecon with Dr. Wiley Chambers, Dr. Lillian Patrician, and Lori Gorski concerning phase 3 statistical plan |
| 12/07/98 | 107 | Allergan letter of understanding following the pre-NDA meeting of 11/16/98 |
| 12/09/98 | NDA | Allergan cover letter for pre-submission of chemistry, manufacturing and control section of NDA 21-023 |

N/A = Not applicable

ALLERGAN

2525 Dupont Drive P.O. Box 19534 Irvine CA 92713-9534 (714) 752-4500

August 26, 1996

Wiley Chambers, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Letter of Understanding, end of phase 2 meeting
Cyclosporine ophthalmic emulsion
IND 32,133

Dear Dr. Chambers:

This letter will record our understanding of the meeting held between Allergan and the Agency on June 4, 1996. The meeting was held to discuss the results of the phase 2 clinical trial on cyclosporine ophthalmic emulsion and to present our current research on ocular surface disease. Present at the meeting were:

| Allergan, Inc. | | FDA | |
|---|---|---|---|
| E. Bancroft | Regulatory Affairs | J. Bull | Medical |
| B. Reis | Clinical Research | T. Carreras | Medical |
| K. Stern | Biostatistics | W. Chambers | Acting Director |
| M. Stern | Biological Sciences | J. Holmes | Project Manager |
| J. Wang | Biostatistics | R. Joyce | Medical |
| | | H. Leung | Biometrics |
| | | M. Weintraub | Office Director (via phone) |
| | | M. Walling | Assistant to Director |

The major points that were discussed include:

To demonstrate efficacy, we must show a one unit (or grade) difference between the active group and the vehicle group; or show a statistically significant difference between a responder group and the vehicle group (as % cured).

> A responder is defined as a patient who goes to zero ('asymptomatic' to be defined in the protocol) in one objective sign and one subjective endpoint.

We must show efficacy in at least one objective sign and one subjective endpoint.

For the subjective endpoint, we can utilize the Ocular Surface Disability Index or the faces chart or pick any one symptom; FDA has no preference.

If we use the Ocular Surface Disability Index, it must be validated.

Data generated by tertiary measures of inflammation will be useful.

There are no safety concerns at the drug levels we are testing.

Because we did not show a clear differentiation in effect among the doses, it was recommended that we include a lower concentration in one phase 3 clinical trial to confirm that we have chosen the lowest effective concentration. 0.05% and 0.1% were suggested as possible concentrations for study.

The 0.2% and 0.4% concentrations gave no additional clinical benefit.

The patient numbers proposed by Allergan, 300 patients on active treatment, are adequate for submission.

Thank you for the opportunity to discuss our research and development programs with you. If there are any questions or comments on this letter, please contact me at phone number (714) 246-4391 or fax number (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (714) 752-4500

December 9, 1996

Wiley Chambers, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion
IND 32,133 - Serial No. 068
Letter of Understanding, end of phase 2 meeting

Dear Dr. Chambers:

This letter will record our understanding of the meeting held between Allergan and the Agency on October 24, 1996. Present at the meeting were:

| Allergan, Inc. | | FDA | |
|---|---|---|---|
| E. Bancroft | Regulatory Affairs | J. Bull | Medical Officer |
| B. Reis | Clinical Research | W. Chambers | Acting Director, HFD-550 |
| K. Stern | Biostatistics | J. Holmes | Project Manager |
| | | H. Leung | Biostatistics |
| | | M.J. Walling | Associate Director, ODE V |
| | | M. Weintraub | Director, ODE V |

The major points discussed at the meeting are listed below:

1. Allergan gave a brief update on changes from phase 2 to phase 3 in the Chemistry area, including the use of the same oil concentration for all formulations. There were no comments by the Agency.

2. Allergan gave an overview of the preclinical safety data package, indicating which studies were completed by Allergan and which were completed by and cross-referenced to Sandoz applications. There were no comments by the Agency.

3. Allergan presented summary information from the phase 2 ocular microbiology results and corrected one summary table which included patient numbers. This updated page will also be filed to the IND as an amendment. Upon the Agency's request, Allergan also presented details of the organisms found in these patients, and confirmed that all data would be filed to the IND. Allergan indicated that collection

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Letter of Understanding
IND 32,133
Page 2 of 3
December 9, 1996

of microbiology data would not be conducted in the phase 3 trial. There were no other comments by the Agency.

4. Allergan outined the phase 3 trial study design. The Agency recommended that after the six months of masked treatment, rather than roll all patients to an open-label study on 0.1% cyclosporine, we continue all patients with their current treatment in a six month treatment-extension phase. There was a discussion of other options for the second six months of the trial. During the discussion, another suggestion from the Agency was that if patients from the vehicle group discontinue during the six month treatment-extension phase due to treatment failure, we switch them to an active drug group at that time. These patients could be randomized to both 0.05% and 0.1% groups, or could all be switched to the 0.1% group.

   However, the Agency indicated that Allergan could choose any of the options discussed, and we should specify our decisions in the final phase 3 protocol.

5. The Agency confirmed that Allergan could file the NDA after completion of the first six months of masked treatment; however, they felt we would gather useful and relevant information from the additional six month treatment-extension phase.

6. Allergan presented a proposal for validation of the Ocular Surface Disability Index (OSDI) instrument for use as a key subjective efficacy variable. The Agency agreed that the scope of Dr. Schiffman's protocol seemed adequate for validation. However, the Agency would not comment on its suitability for use as the key subjective variable in phase 3 until after they had reviewed and approved the final report of the validation study, including the raw data and data analysis. Allergan agreed to file this information to the IND.

7. The Agency indicated that we did not have to to wait for FDA final approval of the OSDI prior to initiating the phase 3 trials. If the validation study data are not adequate, the Agency will accept the facial expressions scale. If we switch to the facial expressions scale, we can justify the change in the Integrated Clinical and Statistical Final Report without compromising the trial and without filing a protocol amendment.

8. A discussion was held on the measurement of the key objective endpoints. The Agency recognizes that there is large variability in Schirmer Tear Test data and that there is great difficulty in interpreting Schirmer data. The Agency does not recommend Schirmer data as the key objective endpoint. The Agency agreed that

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fluorescein staining of the cornea and conjunctiva as Allergan proposed, and the use of the Bron scale for evaluation, is entirely acceptable and preferred.

9. There was further discussion on ways to utilize Schirmer data, especially with respect to correlation with clinical relevance. The Agency recommended we collect the Schirmer data because it might prove supportive, and indicated their willingness to review any proposal we submit for evaluation and interpretation of the data for clinical relevance.

10. A discussion was held on Allergan's questions about global pivotal clinical trials. There were two questions on this topic: one on proportion of patients from different geographic areas; one on race distribution within the study population. The Agency acknowledged Allergan's desire to execute global protocols to support global filings. Their requirement is that the overall study population represent the US population since the Agency will approve the drug for use in the US. They would require an analysis of US data separately from non-US data.

11. Allergan asked about the total number of patients required per site and the Agency recommended we try to enroll not less than 10 patients per arm at each site. If a small number of the sites are unable to reach this goal, data from those sites could be pooled.

These were the major points discussed at this meeting. Thank you for your continued support and guidance on our drug development projects. If there are any questions or comments on this letter, please contact me at telephone number (714) 246-4391 or fax number (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

cc: B. Reis, Allergan
K. Stern, Allergan

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**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

May 21, 1997

Wiley Chambers, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion
IND 32,133 - Serial No. 079
Letter of Understanding, Chemistry, Manufacturng and Controls meeting

Dear Dr. Chambers:

This letter will record our understanding of the meeting held between Allergan and the Agency on April 24, 1997. Present at the meeting were:

| Allergan, Inc. | | FDA | |
|---|---|---|---|
| E. Bancroft | Regulatory Affairs | W. Chambers | Acting Director, HFD-550 |
| J. Kent | Pharmaceutical Sciences | A. Fenselau | Review Chemist |
| O. Olejnik | Product Development | D. Gunter | Project Manager |
| S. Ruckmick | Pharmaceutical Analysis | J. Holmes | Clinical Reviewer |
| | | L. LoBianco | Acting Supervisor, Proj. Mgmt. |
| | | H. Patel | Chemistry Team Leader |
| | | M. Seggel | Review Chemist, HFD-530 |
| | | S. Tso | Review Chemist |

The major points discussed at the meeting are listed below:

1. Allergan proposed that no related substances regulatory specification be applied to the finished dosage form. The Agency indicated a specification will be required; however the Agency and Allergan will work together to develop a reasonable specification. The Agency acknowledged the analytical difficulties with this compound, and advised that Allergan collect additional data and propose a specification at a later date.

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Letter of Understanding, IND 32,133
Page 2 of 3
May 21, 1997

2. Allergan proposed that no regulatory specification for globule size be applied to the finished dosage form. The Agency indicated a specification will be required, and recommended that Allergan continue to collect data and then set a reasonable specification.

3. The Agency was satisfied that globule size at the submicron particle size range was not a stability-indicating parameter, and measurement at submicron size was not required.

4. The Agency recommended Allergan do some additional developmental studies on process control of the emulsion. For example, study the effect of a worst case homogenization time on coalescence of globules in ongoing stability as a positive control.

5. The Agency discussed with Allergan areas in which additional processing studies could prove valuable. One such study might involve the evaluation of emulsion and globule size stability at different or sub-optimal homogenization processing times.

6. The Agency indicated that Allergan should continue collecting globule size data on different product batches to show inter-batch consistency.

7. The Agency made several comments on specific questions asked by Allergan:

   Particulate Matter Testing will not be required as a control test or specification for the finished dosage form.

   The castor oil utilized for the product must be tested to and meet the requirements of the USP monograph.

   The pH specification appears quite wide, and Allergan should provide data to support the specification.

   The carbomer excipient used should be sourced from a benzene-free manufacturing process and be essentially free of benzene residuals.

   The NDA for Cyclosporine ophthalmic emulsion will probably not qualify for a Priority rating, because the drug will not 'cure' the patient.

   An Advisory Panel Meeting to discuss approval of the NDA may occur. This would normally be determined within 15 to 60 days after filing the NDA.

With an apppropriate washout period, patients with previous exposure to a topical cyclosporine formulation may be enrolled in the Allergan phase 3 clinical trial. It was clarified subsequent to this meeting, in a telephone call on May 8, 1997 between Dr. Chambers and Elizabeth Bancroft, that these patients can not have been enrolled in the Allergan phase 2 clinical trial.

8. In a general discussion, the Agency commented that the new Guideline for Stability would be issued for comment soon. The Guideline currently includes a recommendation that time zero data from the commercial manufacturing site for at least one batch at pilot scale be included in the NDA. There is no date currently stated for issuance of this Guideline.

Thank you for the opportunity to discuss our drug development projects with you. As promised during the meeting, samples of freshly manufactured and aged cyclosporine emulsion were recently sent to Dr. Tso.

If there are any questions, or if anything has been stated incorrectly in this letter, please contact me at telephone (714) 246-4391 or fax (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

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**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (714) 752-4500

January 12, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Subject: Cyclosporine ophthalmic emulsion
IND 32,133 - Serial No. 087
Proposed Tradename

Dear Dr. Chambers,

Allergan is developing cyclosporine ophthalmic emulsion for the treatment of keratoconjunctivitis sicca. We are currently evaluating tradenames, and would like Agency comment on the following proposed tradename:

RESTASIS (cyclosporine ophthalmic emulsion) 0.X%

We would appreciate any comment on the suitability of this proposal by March 1998. If you have any questions or need additional information, please contact me at telephone (714) 246-4391 or fax (714) 246-4272.

Thank you for your assistance.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

cc: B. Reis, Allergan

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**ALLERGAN, INC.**
**PHARMACEUTICAL EYECARE REGULATORY AFFAIRS**

**FDA TELEPHONE CONTACT**

| | | | |
|---|---|---|---|
| **TO:** | LIST | **SUBJECT:** | Statistical plan for cyclosporine ophthalmic emulsion |
| **FROM:** | E. Bancroft | **DATE:** | 25 June 1998 |
| **COPIES:** | P. Kresel, B. Reis, K. Stern, J. Wang, File | | |

A telephone conversation was held with the FDA on May 27, 1998 to discuss the proposed statistical plan for cyclosporine ophthalmic emulsion. The following participated: Wiley Chambers, Deputy Director, Lillian Patrician, Biostatistician, Lori Gorski, Project Manager, Brenda Reis, Katherine Stern, James Wang, Elizabeth Bancroft.

The stat plan as proposed was acceptable with the following comments:

1. For the intent to treat analysis, the Agency prefers Last Observation Carried Forward (LOCF).
2. For the per protocol analysis, the Agency prefers observed cases only (currently proposed as LOCF).
3. The Agency stated that at this time they did not necessarily agree that the clinical significance of the Ocular Surface Disease Index (OSDI) should be 0.1. They stated it should probably be higher, but that they were willing to evaluate this again. Allergan indicated that we would file the OSDI validation report to the IND soon.
4. The Agency questioned why the categories within Schirmer's scale are defined differently in the shift table. Allergan explained that this was requested by our European colleagues, but that we would include in the NDA a shift table using the same categories as originally defined.
5. For the global evaluation we can define the dichotomous answer, but the Agency will not accept the break point. They recommended a break at 0 (completely cleared) or 1 (almost cleared, 90% improvement. We should report by individual category also.
6. We should clearly state that Table 35 contains the verbatim comments from the CRFs.
7. For visual acuity in addition to the tables submitted, we should add tabulations of patients for these 7 categories:
   number of patients with >2 lines loss
   number of patients with 2 lines loss
   number of patients with 1 line loss
   number of patients unchanged
   number of patients with 1 line improvement
   number of patients with 2 lines improvement
   number of patients with >2 lines improvement

The incidence in each category should be reported. The shift table is acceptable.

8. Table 3 is not helpful – use COSTART terms only.
9. Dr. Patrician asked for information on the Bootstrap Method of analysis. Allergan agreed to submit a literature reference to the IND. If Allergan uses any internal codes, these should be identified and discussed in the stat report.
10. A subgroup analysis of patients with and without Sjögren's is acceptable. The same efficacy tables are acceptable. This analysis can be included as an appendix.
11. Pooling of certain sites with less than approximately 30 patients is acceptable, as long as each investigator and site is identified.
12. A subgroup analysis for the primary efficacy variables by light and dark irises is also desired.

POST MEETING NOTE

A follow-up email was sent to Dr. Chambers to ask for clarification on what would be an acceptable level of significance for the OSDI. A change of 0.1 (change of 1 unit in 6 of 12 questions) was specified in the protocol and stat plan. Dr. Chambers indicated that he thought that a 1 unit change in each question would be clinically significant.

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

December 7, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products
HFD-550
Food & Drug Administration
9201 Corporate Blvd.
Building 2
Rockville, MD 20850

Dear Dr. Chambers,

RE: IND 32,133
**SERIAL NO. 107**
Cyclosporine ophthalmic emulsion
Letter of understanding, preNDA meeting

This letter will record Allergan's understanding of the preNDA meeting for cyclosporine ophthalmic emulsion held with the Agency on 16 November 1998. Present at the meeting were:

| Agency | | Allergan | |
|---|---|---|---|
| W. Chambers | Deputy Director | E. Bancroft | Regulatory Affairs |
| J. Dunbar | Medical Reviewer | P. Kresel | Regulatory Affairs |
| L. Gorski | Project Manager | B. Reis | Clinical Development |
| J. Holmes | Medical Reviewer | K. Stern | Biostatistics |
| R. Rodriguez | Project Manager | M. Stern | Pharmacology |
| | | L. Thieme | Quality Assurance |

1. Allergan proposed doing a meta-analysis of efficacy across the 2 pivotal clinical studies. The Agency indicated that this type of analysis was not useful. Each study should stand alone and each should meet safety and efficacy criteria.

2. Allergan proposed doing an analysis of efficacy combining both drug concentrations versus vehicle, for each study separately. The Agency indicated it will not base approval on this type of analysis. Dr. Chambers indicated there was more strength in analyses that showed 2 active concentrations to be marginally close than an analysis of 2 concentrations combined showing efficacy.

3. Allergan proposed to file only the 0.05% cyclosporine strength. Dr. Chambers commented that if the data show comparable efficacy [that we are on the response threshold as we believe] and there is no significant difference in safety, then we should consider filing the higher strength, 0.1%.

4. Allergan proposed using corneal staining (not sum of staining) and blurred vision (not the OSDI©) as the primary efficacy variables. There were no objections by the Agency to this proposal.

5. Dr. Chambers indicated he was willing to review all the data that was generated from the tertiary tests.

6. Dr. Chambers requested changes to Table 1, Patient Disposition, and requested a new table on Visual Acuity changes. Attached to this letter are the revised Table 1 and the new Table 39, Visual Acuity: Changes from Baseline. Allergan would appreciate confirmation that these Tables are acceptable for submission.

7. Allergan indicated that the NDA would probably not be filed in December 1998 as planned, but in early 1999.

Thank you for the opportunity to discuss the upcoming NDA for cyclosporine ophthalmic emulsion. If there are any comments or changes to this letter, please contact me at telephone number (714) 246-4391 or fax (714) 246-4272.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

encl.

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

December 9, 1998

Center for Drug Evaluation and Research
Central Document Control
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20857

RE: NDA 21-023; Cyclosporine Ophthalmic Solution, 0.05% and 0.1%
**Pre-Submission: Chemistry, Manufacturing and Control Section**

To Whom It May Concern:

Allergan hereby submits both an archival and review copy of the Chemistry, Manufacturing and Control (CMC) section of NDA 21-023. The subject of this NDA is Cyclosporine ophthalmic emulsion which is indicated for the treatment of moderate to severe keratoconjunctivitis sicca to restore and maintain normal tear secretion and ocular surface integrity. The applicant hereby requests priority review status for this product since it is the first therapeutic product for the treatment of keratoconjunctivitis sicca, and therefore, would provide a significant improvement in the safe and efficacious treatment of the disease.

The active pharmaceutical ingredient (API), Cyclosporine USP, is manufactured by Novartis Pharma AG, located in Basel, Switzerland and Ringaskiddy, County Cork, Ireland. The chemistry, manufacturing and control of the API is reported by Novartis in approved NDA 50-073 and NDA 50-074. A letter authorizing FDA to review the data in these NDAs on behalf of Allergan is enclosed.

The finished drug product is a sterile preservative-free, oil-in-water emulsion containing either 0.05% or 0.1% (w/w) cyclosporine USP. The inactive ingredients are castor oil PhEur, polysorbate 80 NF, carbomer 1342 NF, glycerin USP, sodium hydroxide USP, and purified water USP. The formulation has a target pH of 7.4. The test parameters proposed for the finished drug product to ensure its identity, strength, and quality throughout shelf-life include cyclosporine potency, cyclosporine identification, osmolality, pH, globule size, viscosity, physical appearance, microscopic appearance, and sterility. The primary packaging is a single-use unit dose vial (0.4 mL fill volume in 0.9 mL fill capacity) manufactured as part of a form-fill-seal operation from virgin low-density polyethylene resin. A 24 month expiration dating is proposed for Cyclosporine ophthalmic emulsion, 0.05% and 0.1%, in the proposed marketing configuration when stored at USP controlled room temperature.

NDA 21-023; Cyclosporine Ophthalmic Emulsion. 0.05% and 0.1%
Pre-Submission of CMC Section
December 9, 1998
Page 2 of 2

This NDA file will be supplemented with the following items upon submission of the clinical and non-clinical sections of the NDA:

| Item Number | Description of Item |
|---|---|
| Section 4A.3.4.7 | Completion of the commercial-scale batch results table |
| Appendix 4A.5.3.2 | Aseptic process validation report |

During the development of this product under IND 32,133, staff members of the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products have provided timely review of questions and advice. Allergan, Inc. wishes to express its sincere appreciation for the Agency's consultations during the development of this product.

Allergan asserts that, with the exceptions listed above, all the available information on the chemistry, manufacturing and control of Cyclosporine ophthalmic emulsion is contained in this NDA.

This product is the first for the treatment of keratoconjunctivitis sicca, therefore, Allergan, Inc. asks that this NDA receive priority status review.

Sincerely,

Elizabeth Bancroft
Director, Regulatory Affairs

MB/mkb

## 1.3 DMF REFERENCES

The following Drug Master Files (DMFs) and New Drug Applications (NDAs) are referenced in support of this application. A copy of an authorization letter from each sponsor is enclosed:

| File Type | File Owner | Reference for: |
|---|---|---|
| NDA 50-573 and<br>NDA 50-074 | Novartis Pharmaceuticals<br>Corporation<br>59 Route 10<br>E. Hanover, NJ 07936-1080 | Chemistry, manufacture and control of active pharmaceutical ingredient (API) |
| DMF 11086 - Type I | Allergan, Inc.<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, CA 92623-9534 | Manufacturing site for finished product (Allergan, Inc., Waco, TX) |
| DMF 1572 - Type III | Chevron Chemical Company<br>P.O. Box 7400<br>Orange, TX 77631-7400 | Resin supplier for unit dose vial |

Ronald G. Van Valen
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973-781-7646
Fax 973-781-6325
Internet: ronald.van valen
@pharma.novartis.com

NOVARTIS

April 27, 1998

Elizabeth Bancroft
Allergan Inc.
Regulatory Affairs
2525 Dupont Drive
Irvine, California 92612

**Sandimmune® (cyclosporine USP)**
**2% Ophthalmic Ointment**

**Updated Letter of Cross-Reference**

Dear Ms. Bancroft:

In accordance with request from Dr. Luc Zipper, CMC Manager, Novartis Pharma AG, Basel Switzerland, I am providing the updated list of all relevant and current cyclosporine applications for cross-reference to support the Allergan NDA submission for cyclosporine ophthalmic ointment. Please also refer to the previous communication to FDA, letter dated November 15, 1994, which provided authorization to Allergan to cross-refer to all relevant Sandimmune (cyclosporine, USP) IND and NDA documentation.

Please note that the previous listing (attachment to letter 11/15/94) contained one additional IND application (IND No. 18,629) which is no longer active and has been withdrawn.

If there are comments or questions, please call me at (973) 781-7646.

Sincerely,

Ronald G. Van Valen
Associate Director
Drug Regulatory Affairs

attachment

cc: L. Zipper

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## LIST OF CROSS-REFERENCED INDs and NDAs

| IND No. | DESCRIPTION |
|---|---|
| 32,133 | Sandimmune® 2% Ophthalmic Ointment<br>(IND transfer to Allergan Inc.; letter dated September 29, 1994) |
| 16,450 | Sandimmune® Oral Solution/Soft Gelatin Capsules (cyclosporine, USP)<br>Indication: Prophylaxis of organ rejection<br>Documentation currently resides within the FDA Division of Special Pathogens and Immunologic Drug Products/HFD-590 |

| NDA No. | DESCRIPTION |
|---|---|
| 50-574 | Sandimmune® Oral Solution (cyclosporine oral solution, USP)<br>Indication: Prophylaxis of organ rejection<br>Documentation currently resides within the FDA Division of Special Pathogens and Immunologic Drug Products/HFD-590 |
| 50-573 | Sandimmune® Injection (cyclosporine concentrate for injection, USP)<br>Indication: Prophylaxis of organ rejection<br>Documentation currently resides within the FDA Division of Special Pathogens and Immunologic Drug Products/HFD-590 |

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

**November 6, 1998**

Center for Drug Evaluation and Research
Central Document Room
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

**RE: DMF #11086, Allergan, Inc., Waco, Texas**
**(Type I DMF: Facilities, Personnel and Operating Procedures)**

To Whom It May Concern:

Allergan, Inc., Waco, TX is a division of Allergan, Inc., Irvine, CA. We hereby authorize the Food and Drug Administration to refer to and incorporate by reference, information contained in DMF 11086 in support of the following Allergan application to be submitted to the Agency:

NDA filing for Cyclosporine Ophthalmic Emulsion

I hereby certify that DMF 11086 is current and Allergan will comply with the statements made in the DMF.

This authorization does not constitute public disclosure and confidentiality of the referenced material should be preserved.

If you have any questions regarding this authorization, please contact me at (714) 246-4391.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Director
Regulatory Affairs

EB:mkb

Chevron

December 16, 1993

Chevron Chemical Company
P.O. Box 7400
Orange, TX 77631-7400

E. B. Parker, Ph.D.
Manager, Product Compliance
Technology Department
Phone 409 882 6160
Fax 409 882 6135

FOOD AND DRUG ADMINISTRATION
National Center for Drugs and Biologics
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RE: DRUG MASTER FILE NO. 1572

Gentlemen:

Chevron Chemical Company hereby authorizes the Administration to refer to Drug Master File No. 1572 with regard to our polyethylene resin PE 4538A with respect to all new and supplemental new drug applications filed by Allergan, Inc. of Irving, CA.

We authorize your office to review Chevron Chemical Company's DMF 1572 in support of the application or supplements submitted by Allergan, Inc.

The products supplied to Allergan, Inc. will be manufactured in accordance with DMF 1572 and will comply with Good Manufacturing Practices.

We certify DMF 1572 is current; if changes are made to the DMF, Allergan, Inc. will be notified and DMF 1572 will be amended.

Listed below are all the submission dates, volume and page numbers for PE 4538A:

1/15/82 Volume 1 Pages 101 - 106

Please hold the information in DMF 1572 confidential to the extent possible under 21 CFR 314.430 for the New Drug and Antibiotic Regulations and 21 CFR 20.61 Public Information Regulations.

Yours truly,

E. B. Parker

EBP/crh

cc: Laura Davis
Allergan, Inc.

555-93.FDA V2-1572.131

**ALLERGAN**

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

## 1.4 PATENT INFORMATION AND CERTIFICATION

The following patents are currently in effect for cyclosporin A. A copy of each patent is enclosed.

| Patent number | Patent Title | Expiration Date |
|---|---|---|
| U.S. Patent No. 4,649,047 | Ophthalmic Treatment By Topical Administration Of Cyclosporin | March 19, 2005 |
| U.S. Patent No. 4,839,342 | Method Of Increasing Tear Production By Topical Administration Of Cyclosporin | June 13, 2006 |
| U.S. Patent No. 5,474,979 | Nonirritating Emulsions For Sensitive Tissue | May 17, 2014 |

I, the undersigned, hereby declare that Patent Nos. 4,649,047, 4,839,342 and 5,474,979 covers the formulation, composition, and/or method of use of cyclosporin A. This product is the subject of this application for which approval is being sought.

Peter A. Kresel, MS, MBA (Date)

Sr. Vice President, Global Regulatory Affairs

Allergan, Inc.

**United States Patent** [19]

**Kaswan**

[11] **Patent Number: 4,649,047**

[45] **Date of Patent: Mar. 10, 1987**

[54] **OPHTHALMIC TREATMENT BY TOPICAL ADMINISTRATION OF CYCLOSPORIN**

[75] Inventor: **Renee Kaswan**, Athens, Ga.

[73] Assignee: **University of Georgia Research Foundation, Inc.**, Athens, Ga.

[21] Appl. No.: **713,701**

[22] Filed: **Mar. 19, 1985**

[51] **Int. Cl.**[4] ..... **A61K 37/00; A61K 31/74**

[52] **U.S. Cl.** ..... **424/78; 514/11; 514/885; 514/912**

[58] **Field of Search** ..... 424/78; 514/885, 11, 514/912, 914

[56] **References Cited**

PUBLICATIONS

Chem. Abst. 102:214587v (1985)—Mosteller et al.
Chem. Abst. 102:125267y (1985)—Williams et al.
Chem. Abst. 102:89788h (1985)—Boisjolv et al.
Chem. Abst. 101:103683h (1984)—Chan et al.
Chem. Abst. 101:16979v (1984)—Mannis et al.
Chem. Abst. 97 84951z (1982)—Nussenblatt et al.
Chem. Abst. 97 439c (1982)—Kana et al.
Chem. Abst. 94 185,629u (1981)—Nussenblatt et al.
Amer. J. Ophthal. 96(3) 275-282 (1983)—Nussenblatt et al.
Biosjoly et al., Prophylactic Topical Cyclosporine in Experimental Herpetic Stromal Keratitis, Arch Ophthalmol, 102, 1804, Dec. 1984.
Mosteller et al., Penetration of Topical Cyclosporine into the Rabbit Cornea, Aqueous Humor, and Serum, Arch. Ophthalmol, 103, 101, Jan. 1985.
Nussenblatt et al., Cyclosporin A Therapy in the Treatment of Intraocular Inflammatory Disease Resistant to Systemic Corticosteroids and Cytotoxic Agents, American Journal of Ophthalmology, 96, 275, Sep. 1983.
Kaswan et al., Intraocular Penetration of Cyclosporin in Rabbits, ARVO Abstracts, Investigation Ophthalmol. Supp. 25, 3, p. 38, 1984.

*Primary Examiner*—Douglas W. Robinson
*Attorney, Agent, or Firm*—Oblon, Fisher, Spivak, McClelland, & Maier

[57] **ABSTRACT**

The present invention relates to a method for the treatment of either phacoanaphylactic endophthalmitis or uveitis by administering at least one cyclosporin topically to the eyes. Topical application of cyclosporin provides cyclosporin to the anterior chamber, the posterior chamber and the vitreous body of the eye.

**20 Claims, 6 Drawing Figures**

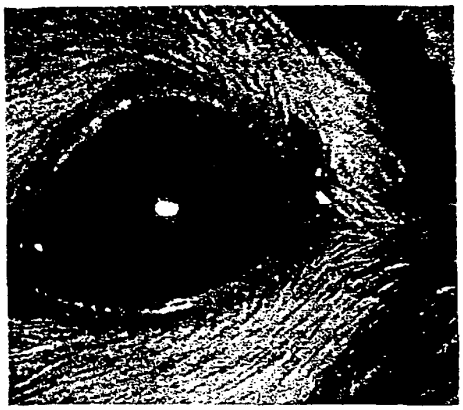

FIG. 1a

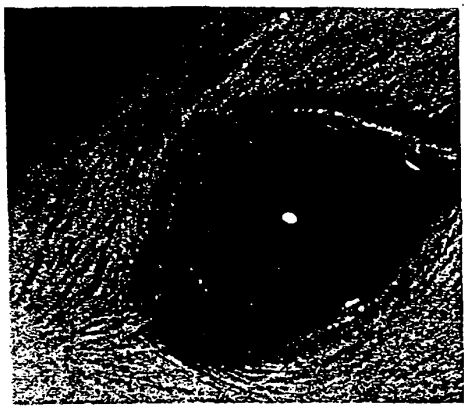

FIG. 2a

FIG. 1b

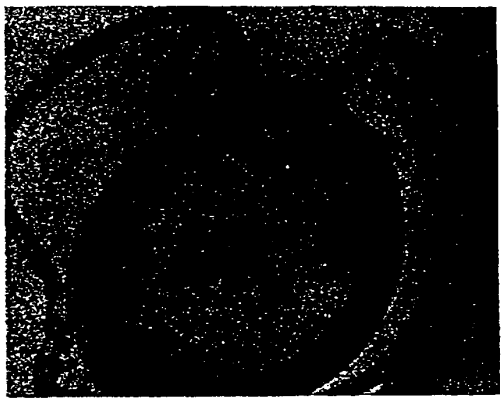

FIG. 2b

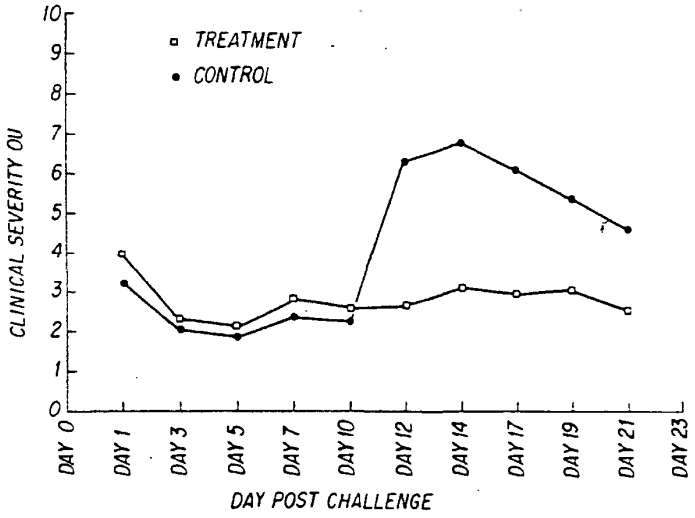
TREATMENT
CONTROL
CLINICAL SEVERITY OU
0
1
2
3
4
5
6
7
8
9
10
DAY 0
DAY 1
DAY 3
DAY 5
DAY 7
DAY 10
DAY 12
DAY 14
DAY 17
DAY 19
DAY 21
DAY 23
DAY POST CHALLENGE

FIG. 3a

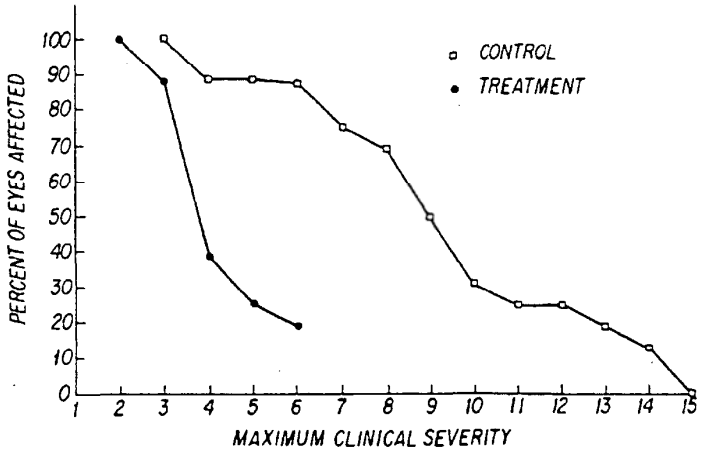
CONTROL
TREATMENT
PERCENT OF EYES AFFECTED
0
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
MAXIMUM CLINICAL SEVERITY

FIG. 3b

# OPHTHALMIC TREATMENT BY TOPICAL ADMINISTRATION OF CYCLOSPORIN

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to cyclosporin treatment of traumatic or surgical phacoanaphylaxis endophthalmitis, or uveitis.

2. Description of the Prior Art

Phacoanaphylactic endophthalmitis and uveitis are diseases of the eye which can be located throughout the eye; in both the posterior and anterior chambers of the eye as well as the vitreous body.

Uveitis, the inflammation of the uvea, is responsible for about 10% of the visual impairment in the United States. Phacoanaphylactic endophthalmitis is a human autoimmune disease.

Panuveitis refers to inflammation of the entire uveal (vascular) layer of the eve. Posterior uveitis generally refers to chorioretinitis and anterior uveitis refers to iridocyclitis. The inflammatory products (i.e., cells, fibrin, excess proteins) of these inflammations are commonly found in the fluid spaces of the eye, i.e., anterior chamber, posterior chamber and vitreous space as well as infiltrating the tissue imminently involved in the inflammatory response. Uveitis may occur following surgical or traumatic injury to the eye; as a component of an autoimmune disorder, i.e., rheumatoid arthritis, Behcet's disease, ankylosing spondylitis, sarcoidosis; as an isolated immune mediated ocular disorder, i.e., pars planitis, iridocyclitis etc., unassociated with known etiologies; and following certain systemic diseases which cause antibody-antigen complexes to be deposited in the uveal tissues. Together these disorders represent the non-infectious uveitities.

The normal eye is protected from immune surveillance by blood barriers which do not allow free migration of cells or proteins into the eye. When the eye is injured or when vasculitis occurs, the internal ocular structures are exposed to the general immune system and frequently elicit autoimmune responses.

Phacoanaphylaxis is a severe form of uveitis in which the lens is the causitive antigen. The lens proteins are normally secluded by the lens capsule since before birth. When these proteins are released into the eye by injury or surgery or occasionally during cataract development, they can become intensely antigenic and incite an autoimmune response. If the response is moderate it is seen as a chronic uveitis. If it is very fast in progression they eye becomes severely inflamed in all segments. This latter response is named phacoanaphylaxis.

Cyclosporins are unique immunosuppressive agents derived from an extract of soil fungi. Cyclosporine A was first proposed for use as an antifungal agent but its immunosuppressive effects were found to be more marked than its antibiotic potential. This drug inhibits the generation of effector T-lymphocytes without inhibiting the expression of suppressor lymphocytes.

Cyclosporin's immunosuppressive properties has led to its use in immune system related diseases. In ophthalmic applications, cyclosporin has been used topically for the treatment of eye surface (e.g., cornea) related diseases.

For example, Hunter et al (*Clin. Exp. Immunol.* (1981), 45, pp. 173–177) has administered cyclosporin topically in a rabbit model of corneal graft rejection with positive results. These effects were found to be attributable to T-cell suppression within the eye or within systemic compartments such as blood or lymph.



Boisjoly et al (Arch. Ophthalmol. (1984) 102:1804–1807) have reported that topical application of Cyclosporine had a beneficial prophylactic effect towards the treatment of severe herpetic stromal keratitis.

Mosteller et al (*Investigative Ophthalmol.* (1984) Supp. 23, 3, p. 38) propose the potential suppression of deleterious ocular immune reactions such as the eye surface cornea allograft reaction by applying a single dose of a 10% Cyclosporine A ointment in the lower culde-sac of rabbit eyelids.

In other ophthalmic applications, where the disease being treated is not limited to the eye surface, cyclosporin has been used systemically.

For example, Nussenblatt et al (*Amer. J. Ophthamol.* (1983), 96, pp. 275–282) has reported clinical improvement in some patients with noninfectious posterior uveitis following systemic treatment with Cyclosporin.

To date, uveitis has been treated by systemic administration of cyclosporin since this disease is not limited to the eye surface. However, systemic therapy with cyclosporin has serious drawbacks. First there is a high risk of adverse responses when cyclosporin is used systemically. For example, cyclosporin increases the severity of epithelial disease when antiviral coverage is not provided. Cyclosporine used systemically has also been associated with a high incidence of renal toxicity, some cases of hepatotoxicity, increased incidence of lymphoid tumors and increased incidence of opportunistic infections. It is only slightly less toxic than other immunosuppressive agents i.e., cyctoxan, aziothioprine which in addition to causing increased incidence of infections, are more irreversible in their effects than is cyclosporine. The systemic side effects of cyclosporine are so severe and so common that they preclude its use to life-threatening or in some cases severe sight-threatening disease. Finally, systemic application of cyclosporin is limited by its prohibitive cost.

Prior art understanding of the activity of cyclosporin towards ophthalmic traumatic uveitis has however rested on the theory that total body immunosuppression was necessary for efficacy. By requiring systemic administration in cyclosporin treatment of opthalmic diseases not limited to the eye surface, a patient has heretofore been required to assume a high risk of adverse immunological responses, this risk naturally being accompanied by high treatment expense due to the quantities of cyclosporin required in systemic therapy.

Accordingly there exists a strong need for the elimination of the undesirable physiological and economic problems associated with cyclosporin treatment of phacoanaphylactic endophthalamitis and uveitis, while maintaining the advantageous therapeutic properties of this treatment.

Applicants have now surprisingly discovered that although current ocular pharmacology dictates that topical medications in general are not useful for the treatment of opthalmic diseases found in the posterior or vitreous segments of the eye (see, e.g., Maurice et al, *Ocular Pharmacokinetics, in Pharmacology of Eye*, Sears, M. L., editor, Springer-Verlag publisher, New York (1984), pp. 19–102), the topical administration of a cyclosporin to the eye is efficatious in the treatment of phacoanaphylactic endophthalmitis or uveitis found

either in the anterior or posterior chambers of the eye or in the vitreous body of the eye.

## SUMMARY OF THE INVENTION

Accordingly it is an object of this invention to provide a method for the treatment of phacoanaphylactic endophthalmitis.

It is another object of this invention to provide a method for the treatment of uveitis.

It is another object of this invention to provide a cyclosporin-based treatment of phacoanaphylactic endophthalmitis without the accompanying adverse physiological responses and economic difficulties.

It is another object of this invention to provide a cyclosporin-based treatment of uveitis without the accompanying adverse physiological responses and economic difficulties.

It is another object of this invention to provide a method for the treatment of phacoanaphylactic endophthalmitis in the anterior chamber of the eye.

It is another object of this invention to provide a method for the treatment of uveitis in the anterior chamber of the eye.

It is another object of this invention to provide a method for the treatment of phacoanaphylactic endophthalmitis in the posterior chamber of the eye.

It is another object of this invention to provide a method for the treatment of uveitis in the posterior chamber of the eye.

It is another object of this invention to provide a method for the treatment of opthalmic diseases, such as phacoanaphylactic endophthalmitis or uveitis, found in the vitreous body of the eye.

Applicants have discovered that these objects of the present invention are surprisingly satisfied by the topical application of at least one cyclosporin to the eye. Applicants have discovered that the topical application of at least one cyclosporin in a suitable medical excipient is advantageously useful for the treatment of phacoanaphylactic endophthalmitis or uveitis throughout the globe of the eye.

## BRIEF DECRIPTION OF THE FIGURES

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying figures, wherein:

FIG. 1*a* is a photograph of the clinical appearance of endophthalmitis in a pre-sensitized and untreated rat eye 9 days after lens injury.

FIG. 1*b* is a photograph of the microscopic appearance (×23) of phacoanaphylaxis from an untreated control rat eye.

FIG. 2*a* is a photograph of the clinical appearance, at 14 days, of a rat eye given topical cyclosporine therapy beginning on the day of lens injury.

FIG. 2*b* is a photograph of a microscopic section (×23) of a rat eye 14 days following Cyclosporine topical therapy.

FIG. 3*a* is a graphic representation of the average intraocular inflammation observed in rabbit eyes treated with a topical application of 2% cyclosporine (○) compared to untreated eyes (●).

FIG. 3*b* illustrates the data of FIG. 3*a* in another form; the percentage of eyes reaching a peak of inflammation at any point during a period of 15 days.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method for the treatment of phacoanaphylactic endophthalmitis or uveitis occuring throughout the globe of the eye by topical administeration of a cyclosporin to the eye. This topical application of a cyclosporin provides cyclosporin treatment for the anterior chamber, the posterior chamber and the vitreous body of the eye.

Phacoanaphylactic endophthalmitis and uveitis are diseases of the eye which can be found throughout the eye. In accordance with prior art wisdom, uveitis has been treated via systemic administration of cyclosporin. No treatment method for phaconaphylactic endophthalmitis has been reported. Systemic therapy of any disease with cyclosporin suffers from at least two major drawbacks; a high risk of immunologically related adverse responses and high cost.

Against the wisdom of the prior art, the present inventors have surprisingly discovered that systemic administration of cyclosporin is not necessary for the treatment of uveitis, and additionally that phacoanaphylactic endophthalmitis can be treated. This present invention relates to the unexpected discovery that topical cyclosporin administration to the eyes is very efficatious in the treatment of both of these diseases in various regions of the eye.

The present inventors investigated the levels of cyclosporin present in various parts of the eye as a function of varying administration methods. In this investigation the ocular penetration of cyclosporine following topical or oral administration was determined using radio-immune assays (RIA).

The results of this study, tabulated in the Table below, are given to illustrate the invention only and are not intended to impose any limit thereon.

TABLE

| | Route of Cyclosporine administration vs Tissue Level Cyclosporine (ng/gm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Tissue Cornea | Aqueous | Lens | Anterior Vitreous | Posterior Vitreous | Blood | # Eyes |
| Oral 20 mg/kg/day × 4 days | <250 | <60 | <250 | <60 | <60 | 617 | 12 |
| Ophthalmic 2% oil Q 15 min × 6 | 6,640 (3,600–11,600) | <60 (ND) | <250 | <60 | <60 | ND | 8 |
| Ophthalmic 2% ointment Q 15 min × 6 | 9,750 (5,600–14,400) | <60 (20) | <250 | 325 (80–1,450) | 690 (425–800) | ND | 6 |
| Ophthalmic 2% oil | 15,140 (7,300–27,500) | <60 (24) | <250 | 2,400 (500–4,700) | 400 (250–525) | ND | 8 |

TABLE-continued

| | Route of Cyclosporine administration vs Tissue Level Cyclosporine (ng/gm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Tissue Cornea | Aqueous | Lens | Anterior Vitreous | Posterior Vitreous | Blood | # Eyes |
| QID × 21 d Ophthalmic 2% oil QID × 21 d | 7,400 (7,000–8,200) | 200 (180–200) | 1,340 | 875 (800–950) | 720 (640–800) | ND | 2 |
| | | | | | | | Total = 36 eyes |

Legend:
ND = not determined
QID = 4 times daily
Q 15 min × 6 = every 15 minutes for 6 applications
d = day
ng/gm = nanograms per gram or ml of ocular tissue
values in parenthesis represent the range of the measurements

As can be seen from the Table the topical administration of Cyclosporine at varying dosage schedules provides much greater levels of cyclosporine in various tissues of the eye than is available through oral administration.

Thus topical administration has surprisingly been found to be an excellent method for providing cyclosporin in much greater concentrations to the cornea, lens, anterior vitreous, posterior vitreous, iris and ciliary body regions of the eye, where these higher concentrations of cyclosporin provide a much more effective treatment for phacoanaphylactic endophthalmitis and uveitis in these regions of the eye. Additionally since by its very nature, topical administration does not require cyclosporine dispersion throughout the system as is the case with systemic administrations, the present invention provides a means for directing cyclosporin to the desired location.

The graphs of FIGS. 3*a* and 3*b* demonstrate the efficacy of topical cyclosporine administration.

The graph of FIG. 3*a* plots the intraocular inflammation produced by the intravitreal injection of human serum albumin into rabbit eyes. In this study 16 rabbits, 32 eyes, were used. Eight rabbits received no treatment bilaterally, the other eight rabbits received treatment via the topical administration of 2% cyclosporine in oil bilaterally. The degree of intraocular inflammation was graded clinically 3 times per week for 3 weeks. The scale used to evaluate the eyes is reproduced on page 22. The degree of inflammation, 0 to 4, of each segment of the eye was summed on each day, giving a possible range of inflammation of 0–20 per day. The data graphed represents the average daily inflammation seen in the untreated eyes (●) versus the treated eyes (○).

Both untreated and treated eyes developed a low level of inflammation. The inflammation in the treated eyes never exceed this low level base. By contrast, the untreated eyes which began with the same low level of inflammation had become severely inflammed by the tenth day. This severe inflammation began at about 7 days, peaked at 14 days, and then subsided naturally after day 21.

The graph of FIG. 3*b* illustrates the same data differently. FIG. 3*b* indicates the percentage of eyes reaching a peak inflammation at any point during the experiment. As illustrated, the peak inflammation seen in any untreated eye was 6.0 and the lowest peak level was 2.0. 75% of the treated rabbit eyes never developed any inflammatory response above 5/20. By contrast, the worst inflammatory response in the untreated eyes reached a peak inflammation of 15/20 or greater at some point. The higher degree of inflammation observed in each untreated eye results in a concomitantly greater risk of permanent visual damage.

In accordance with the present invention, the cyclosporin may be used in any efficatious concentration, e.g., 0.1 to saturation (e.g., >20 wt %) in a medically suitable excipient. Such medically suitable excipients may be, for example, animal oil, vegetable oil, an appropriate organic or aqueous solvent, a natural or synthetic polymer or an appropriate membrane.

Examples of these medically suitable excipients may be, for example, olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol (e.g., ethanol, n-propyl alcohol, iso-propyl alcohol), methylcellulose, liposomes or liposome-like products or a silicone fluid. Dimethyl sulphoxide and olive oil are especially preferred. Of course mixtures of at least two of any of the excipient may be used.

An example of a useful polymeric excipient may be, e.g., polyoxyethylated castor oil.

Examples of medically suitable membranes which may be used in the practice of this invention are: microdone, an artificial lipid membrane, polyvinylalcohol or methyl cellulose.

The cyclosporin may be topically administered as an ophthalmic drop or ophthalmic ointment containing an effective amount of the cyclosporin. Concentrations of 0.10 to 20 wt % of cyclosporin may be used.

In accordance with the method of the present invention, cyclosporin may be topically administered in any quantity required to provide the degree of treatment needed. Cyclosporin within the range of 5 microliters to 1000 microliters may be used, e.g., 5 microliters to 1 milliliter of solution or ointment.

The cyclosporin which are useful in the practice of the present invention may be both natural or synthetic cyclosporin. For example, cyclosporin A may be used in the practice of the present invention. Other forms of cyclosporins (e.g., isomers) may also be used. Mixtures of at least two different cyclosporin may be used. The only thing that is required, is that the cyclosporin possess the required activity vis-a-vis phacoanaphylactic endophthalmitis or uveitis.

The method of the present invention is useful in that it can locally prevent activation of a presystemic response. It is useful therapy for traumatic phacoanaphylaxis and iatrogenic lens induced uveitis such as occurs in extracapsular cataract surgery.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for purposes of illustra-

tion of the invention and are not intended to be limiting thereof.

In the following examples tests were performed on animals which are well known models for human opthalmic problems, and/or diseases.

Referring now to the figures, where like reference numerals or letters designate identical or corresponding parts throughout the several views,

FIG. 1*a* presents the clinical appearance of endophthalmitis in a pre-sensitized untreated rat eye 9 days after lens injury. From this photograph it can be seen that neovascularization of the cornea and dense leukophilic reaction in the corneal stroma obscure the inner eye.

FIG. 1*b* presents the microscopic appearance of phacoanaphylaxis from an untreated control rat eye. Zonal distribution of neutrophils and macrophages are apparent around the ruptured anterior lens capsule (see arrow in the figure). Dense lymphocytic effusion fills the vitreous and aqueous space as well as infiltrating the uveal tissue anteriorly and posteriorly. A fibrocytic cyclitic membrane (C) has formed posterior to the lens (l). The globe of the eye is approximately 30% reduced in size due to phthisis.

FIG. 2*a* is the clinical appearance at 14 days of a rat eye given topical cyclosporin therapy beginning on the day of lens injury. Apparent iris blood vessels are normally visualized due to albinism. The eye is otherwise unaffected clinically.

FIG. 2*b* is a microscopic section of a rat eye following 14 days of cyclosporine topical therapy. The anterior lens capsule is ruptured. Subjacent cortical vacuolization and early cataractous change is evident (see arrow in figure). A minimal number of lymphocytes are seen in the iris.

## EXAMPLE 1

The lens-induced granulomatous endophthalmitis (ELGE) model (See Marak, G.E. et al, *Ophthal. Res.* (1978) 10:30) was reproduced in 4/8 control eyes. In contrast, eyes treated topically with Cyclosporine uniformly failed to develop marked cellular infiltration following rupture of the lens capsule. Rats treated with systemic Cyclosporine showed modest protection compared to untreated rats. Although no animals were followed after Cyclosporine withdrawal, it is likely that lens removal could alleviate a need for chronic treatment. Based on the prophylactic effect of topical cyclosporin against development of ELGE, topical Cyclosporine penetration the globe in therapeutic levels is indicated.

Eleven female adult Wistar Furth rats were immunized subcutaneously on 3 occasions every two weeks with 1 ml of a 50:50 mixture of 10 mg homologous lens protein in saline and Freund's complete adjuvant. Two weeks after the last immunization, the rats were anestitized with Ketamine HCl 10 mg/kg intramuscularly. With the aid of a disecting microscope, a sterile 26g needle was introduced through the central cornea and a "Z" shaped anterior lens capsule tear was formed by manipulating the needle in each right eye. Tobrex® ointment was applied post operatively and tetracycline 400 mg/liter was added to the drinking water.

Four rats served as controls and received no antiinflammatory drugs. Four rats received 10 mg/kg cyclosporin 2% in olive oil by gavage beginning two hours post-operatively. Three rats received 15 μl of 2% Cyclosporine in olive oil applied topically 9-12 times daily for three days following injury, then 4 times daily thereafter. After 7 days, the left lens capsules were torn as above in all rats. In the second surgical trial, rats in treatment groups began Cyclosporine per os or topically three hours prior to injury of the second eye.

All rats were examined periodically with a slit lamp or disecting microscope. Fourteen days after the initial surgery all rats were euthanized with halothane® anesthetic. Both eyes were fixed in formalin, processed by standard methods, and stained with hematoxylin and eosin.

Immediately post-operatively, all rats developed a plasmoid aqueous and miosis lasting 48 to 72 hours. Six of eight untreated eyes continued to develop severe uveitis beginning with hypopyon and corneal edema. Four of eight developed secondary glaucoma with buphthalmos. Progression continued with development of corneal abcessation, neovascularization and panophthalmitis (FIG. 1*a*). Four eyes progressed to a phthesis bulbi. Histopathology of these eyes revealed a aseptic gramulomatous panophthalmitis. A zonal distribution of neutrophils and macrophages occurred around the ruptured lens capsule where early cataractrous changes were evident. A cyclictic membrane formed behind the lenses. The anterior chamber, iris, vitrus humor and retina were densely infiltrated with lymphocytes (FIG. 1*b*). On histopathologic examrnation, two untreated eyes have moderate acute anterior uveitis. Two untreated eyes had no inflammation at seven or fourteen days post injury.

None of the 6 eyes treated with topical Cyclosporine developed prolonged or destructive inflammation (FIG. 2*a*). At forty-eight hours post operatively, one eye had a small central corneal abcess which resolved by day five. On histopalogic examination, the lens capsules were torn and the subjacent lens cataractous, but little or no inflammation was associated with the injury (FIG. 2*b*). No difference was noted between the eye begun on therapy 2 hours pre or post trauma.

The rats given oral Cyclosporine developed uveitis intermediate in intensity between controlled and topically treated eyes. Clinically the degree of anterior uveitis appeared most marked at 4 to 6 days in this group after which sometimes lessened. After 7 to 14 days, histopathologic sections of orally treated eyes revealed ⅜ with phacoanaphylasis, ⅜ with anterior uveitis and 2/8 not inflammed.

## EXAMPLE 2

### Cyclosporin distribution as a function of administration method

Intraocular concentrations of cyclosporine as a function of administration route was determined for the blood and the following various eye compartments: cornea, aqueous, lens, anterior vitreous and posterior vitreous.

Methods:

Oral 20 mg/kg/day for 4 or ten days. No intraocular cyclosporine was detected.

Topical application of 17 microliters of 2% cyclosporine in olive oil, applied every 15 minutes for 6 applications, followed by a period of 60 minutes to allow absorption.

Topical application of 2% cyclosporine in oil every 60 minutes for 6 applications, followed by 60 minutes to allow absorption.

Topical application of 100 microliters of 2% cyclosporine in petroleum jelly and mineral oil, applied every 15 minutes for 6 applications, followed by a period of 60 minutes to allow absorption.

Topical application of 2% cyclosporin in olive oil 4 times daily for 10 days.

Following dosage the rabbits were euthanized and the eyes were enucleated and frozen. The eyes were dissected into their component parts. These were then disgested in collagenase and the solutions were analyzed with Radioimmunoassay for cyclosporine content.

Results:

The Table below tabulates the number of eyes subjected to each dosage regime and the range of values obtained for each compartment.

TABLE

| | Route of Cyclosporine Administration vs Tissue Level Cyclosporine (ng/gm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Tissue Cornea | Aqueous | Lens | Anterior Vitreous | Posterior Vitreous | Blood | # Eyes |
| Oral 20 mg/kg/day × 4 days | <250 | <60 | <250 | <60 | <60 | 617 | 12 |
| Ophthalmic 2% oil Q 15 min × 6 | 6,640 (3,600–11,600) | <60 (ND) | <250 | <60 | <60 | ND | 8 |
| Ophthalmic 2% oil Q 60 min × 6 | 9,750 (5,600–14,400) | <60 (ND) | <250 | 325 (80–1,450) | 690 (425–800) | ND | 6 |
| Ophthalmic 2% oil Q 15 min × 6 | 15,140 (7,300–27,500) | <60 (24) | <250 | 2,400 (500–4,700) | 400 (250–525) | ND | 8 |
| Ophthalmic* 2% oil QID × 10 d | 7,400 (7,000–8,200) | 200 (180–200) | 178 | 875 (800–950) | 720 (640–800) | ND | 10 |
| | | | | | | | Total = 36 eyes |

*iris and ciliary body 749, retina 483.
Legend:
ND = not determined
QID = 4 times daily
Q 15 min × 6 = every 15 minutes for 6 applications
d = day
ng/gm = nanograms per gram or ml of ocular tissue
values in parenthesis represent the range of the measurements

## EXAMPLE 3

In another experiment, 1% tritiated cyclosporine in oil was applied to the eyes every 15 minutes for 6 applications followed by 60 minutes to allow for absorption. 3 rabbits, 6 eyes, were used. The eyes were frozen, dissected and digested as above, but this time the RIA was not necessary since the radiolabel was incorporated into the dose applied. The samples were counted in liquid scintillation and the absorbed cyclosporine calculated from the relative radioactivity of each sample. In this experiment the corneal level was 5792 ng/gm, aqueous 143, Iris 95, vitreous 190, lens 0, retina 0. These levels are essentially those found in the lst dosage regimen which used a similar interval but a two-fold higher concentration. This final experiment confirms the accuracy of the method of example 2.

## EXAMPLE 4

Effectiveness of topical cyclosporine administration

Sixteen rabbits, 32 eyes were injected intravitreally on day 1 with 500 micorgrams of human serum albumin. Eight rabbits received no treatment. The other rabbits received 10 microliter of 2% cyclosporine in olive oil applied topically to both eyes 4 times daily beginning 1 hour after albumin injection. The degree of intracular inflammation produced was graded clinically 3 times a week for 3 weeks. The scale used to evaluate the eyes is given below.

| Scheme for Grading Uveitis in Animals injected with Human Serum Albumin | | | | | |
|---|---|---|---|---|---|
| Clinical observation | 0 | +1 | +2 | +3 | +4 |
| Ciliary-scleral injection | none | trace | mild | moderate | severe |
| Corneal clarity | clear | trace edema | mild edema | moderate | severe |
| Iris injection | none, pupil normal | trace | mild | moderate | severe, pupil fixed |
| Anterior chamber haze | clear | trace | mild | moderate ± few KP's | Opaque ± many KP's |
| Viteous & retina | Chorioretinal detail sharp | Chorioretinal detail visible but blurred | fair red reflex | poor red reflex | no red reflex |

Note:
Corneal neovascularization
retinal detachments
hypopyon
hyphena
fibrin deposition
iris bombe, depth of anterior chamber

The degree of inflammation, 1–4 of each regiment of the eye was summed on each day, giving a possible

range of inflammation of 0–20 per day. The data obtained is provided in FIGS. 3*a* and 3*b*.

Method (for Example 4):

Human serum albumin (HSA) induced uveitis was initiated bilaterally (OU) in 16 adult female albino rabbits. The animals received ketamine 25 mg/kg and xylazine 3 mg/kg IM 20 minutes prior to intraocular injections. To prevent vitreal extravasation an aqueous paracentesis was performed with a 30-gauge needle and 0.10 ml aqueous was removed prior to intravitreal injection of 500 micrograms of HSA in 0.10 ml of saline. The subsequent induction and resolution of uveitis were observed by slit-lamp examination and indirect ophthalmoscopy 3 times per week. The degree of inflammation in eyes was graded and summed to give a total daily score of 0–20/eye. All observations were performed without knowledge of treatment group.

The treatment group consisted of 8 rabbits which received 10 microliters of cyclosporine (Sandimmune®), 2% in olive oil applied to the dorsal limbus OU, 4 times daily (QID) beginning 1 hour post HSA injection. The remaining 8 rabbits received no therapy (positive control group). As a negative control group, an additional 4 rabbits were injected intravitreally OU with 0.10 ml of saline without HSA and treated unilaterally with 2% Cs-A as above. Oxytetracycline 1 gm/gallon was added to the drinking water of all rabbits as prophylaxis for Pasteurella respiratory infections. All animal utilization adhered to the ARVO resolution on the use of animals in research. The limulus lysate test (Whittaker Bioproducts Inc) was performed on 3 commercial preparations of HSA and found to be positive in all samples. The HSA used for all rabbits for induction of uveitis had 0.17 endotoxin units /mg HSA.

Obviously, numerous modifications and variations in the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. A method for the treatment of phacoanaphylactic endophthalmitis in the anterior or posterior segment of an eye which comprises administering a therapeutically effective amount of a cyclosporin topically to said eye.

2. A method for the treatment of uveitis in the anterior or posterior segment of an eye which comprises administering a therapeutically effective amount of a cyclosporin topically to said eye.

3. The method of claim 1 wherein from 0.1 to 50 wt % of cyclosporin in a medically suitable excipient is used.

4. The method of claim 2 wherein from 0.1 to 50 wt. % of cyclosporin in a medically acceptable excipient is used.

5. The method of claim 3 wherein the medically suitable excipient comprises animal or vegetable oil.

6. The method of claim 4 wherein the medically suitable excipient comprises animal or vegetable oil.

7. The method of claim 3 wherein the medically suitable excipient comprises olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol, silicone fluid or a mixture thereof.

8. The method of claim 4 wherein the medically suitable excipient comprises olive oil, arachis oil, liposome, castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol, silicone fluid or a mixture thereof.

9. The method of claim 1 wherein the cyclosporin is a natural cyclosporin or a synthetic cyclosporin.

10. The method of claim 2 wherein the cyclosporin is a natural cyclosporin or a synthetic cyclosporin.

11. The method of claim 3 wherein the medically suitable excipient comprises polyvinyl alcohol, polyoxethylated castor oil or methyl cellulose or a mixture thereof.

12. The method of claim 4 wherein the medically suitable excipient comprises polyvinyl alcohol, polyoxethylated castor oil, methyl cellulose or a mixture thereof.

13. The method of claim 7 wherein the medically suitable excipient is dimethyl sulphoxide.

14. The method of claim 8 wherein the medically suitable excipient is dimethyl sulphoxide.

15. The method of claim 1, wherein Cyclosporin A is used.

16. The method of claim 2, wherein said cyclosporin is Cyclosporin A.

17. The method of claim 1, wherein said phacoanaphylactic endophthalmitis is traumatic phacoanapylactic endothalmitis.

18. The method of claim 2, wherein said uveitis is iatrogenic-lens-induced uveitis.

19. A method for the treatment of a disorder caused by excessive immune activity in the anterior or posterior segment of an eye, which comprises topically administering to said eye an amount of a cyclosporin sufficient to reduce said immune activity.

20. A method for the treatment of a disorder caused by excessive immune activity in the vitrous body of an eye, which comprises topically administering to said eye an amount of a cyclosporin sufficient to reduce said immune activity.

* * * * *

United States Patent [19]
Kaswan

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# [54] METHOD OF INCREASING TEAR PRODUCTION BY TOPICAL ADMINISTRATION OF CYCLOSPORIN

[75] Inventor: Renee Kaswan, Athens, Ga.

[73] Assignee: University of Georgia Research Foundation, Inc., Athens, Ga.

[*] Notice: The portion of the term of this patent subsequent to Jun. 13, 2006 has been disclaimed.

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*Primary Examiner*—Delbert R. Phillips
*Assistant Examiner*—T. D. Wessendorf
*Attorney, Agent, or Firm*—Kilpatrick & Cody

[57] ABSTRACT

The present invention provides a method of treating an aqueous-deficient dry eye state in a patient suffering therefrom, which method includes the step of administering cyclosporin topically to the patient's eye. The cyclosporin is administered as a solution, suspension or ointment in a pharmaceutically acceptable excipient.

18 Claims, No Drawings

# METHOD OF INCREASING TEAR PRODUCTION BY TOPICAL ADMINISTRATION OF CYCLOSPORIN

## FIELD OF THE INVENTION

The present invention relates to a method of increasing tear production in a patient suffering from deficient tears in the eye due to an autoimmune dysfunction of the lacrimal (tear) glands. More specifically, this invention relates to a method of treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom, which method includes administering a cyclosporin topically to the patient's eye.

## BACKGROUND OF THE INVENTION

The exposed part of a normal eye is covered by a thin tear film. The presence of a continuous tear film is important for the well-being of the corneal and conjunctival epithelium and provides the cornea with an optically high quality surface. In addition, the aqueous part of the tear film acts as a lubricant to the eyelids during blinking of the lids. Furthermore, certain enzymes contained in the tear fluid, for example immunoglobulin A, lysozyme and beta lysin, are known to have bacteriostatic properties.

A sound lacrimal system functions to form and maintain a properly structured, continuous tear film. The lacrimal apparatus consists of the secretory system (the source), the distribution system and the excretory system (the sink). In the secretory system, aqueous tears are supplied by the main and accessory lacrimal glands.

The bulk of the tear film is made of such aqueous tears. The continuous production and drainage of aqueous tear is important in maintaining the corneal and conjunctival epithelium in a moist state, in providing nutrients for epithelial respiration, in supplying bacteriostatic agents and in cleaning the ocular surface by the flushing action of tear movement.

Abnormalities of the tear film include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca or KCS).

In relatively mild cases, the main symptom of KCS is a foreign body sensation or a mild "scratchiness". This can progress to become a constant, intense burning or irritative sensation which can be debilitating to the patient.

More severe forms progress to the development of filamentary keratitis, a painful condition characterized by the appearance of numerous strands or filaments attached to the corneal surface. Recent evidence suggests that these filaments represent breaks in the continuity of the normal corneal epithelial cells. The shear created by lid motion pulls these filaments, causing pain. Management of this stage of KCS is very difficult.

A frequent complication of KCS is secondary infection. Several breakdowns in the eye's normal defense mechanism seem to occur, presumably attributable to a decrease in the concentration of antibacterial lysozyme in the aqueous tears of a patient suffering from KCS.

Although KCS can develop in the absence of any other overt systemic abnormality, there is a frequent association of KCS with systemic disease. KCS can occur as part of a larger systemic involvement known as Sjogren's syndrome. This classically consists of the triad of dry eyes, dry mouth, and arthritis.



Histologically in KCS (as part of Sjogren's syndrome or in isolation), the initial changes seen in the lacrimal gland are those of focal lymphocytic and plasma cell infiltrates associated with degeneration of glandular tissue. These changes resemble those seen in autoimmune disease in other tissue, giving rise to the speculation that KCS has an autoimmune basis.

Sjogren's syndrome is recognized as an exocrine gland dysfunction. Characteristically, the lacrimal glands show a mononuclear-cell infiltration that ultimately leads to destruction of the glandular structure.

Conventional treatment of KCS is symptomatic.

Normally, aqueous-deficient dry eye states are treated by supplementation of the tears with artificial tear substitutes. However, relief is limited by the retention time of the administered artificial tear solution in the eye. Typically, the effect of an artificial tear solution administered to the eye dissipates within about thirty to forty-five minutes. The effect of such products, while soothing initially, does not last long enough. The patient is inconvenienced by the necessity of repeated administration of the artificial tear solution in the eye as needed to supplement the normal tears. Moreover, such treatment merely acts to alleviate the symptoms of the dry eye state and does not cure any underlying disorders or causes of the dry eye state.

Histologic studies of the lacrimal glands in patients suffering from Sjogren's syndrome have shown some evidence of lacrimal gland inflammation. Such inflammation may simply be due to the normal aging of the patient. It has been suggested that the use of antiinflammatory agents might serve to decrease the glandular inflammation. The systemic use of corticosteroids has been advocated in these conditions. However, the merit of systemic corticosteroids in dry eye states has not been established. In most dry eye cases the hazards of long term use of antiinflammatory agents would seem to outweigh their potential merit.

Surgical procedures have also been suggested in the management of dry eye states. Where there has been significant conjunctival destruction, mucuous membrane transplants have been advocated. It has also been suggested that parotid (saliva) duct transplantation can be useful in the management of dry eyes. However, since surgical alterations to combat dry eye conditions constitute such a drastic remedy and the benefit resulting from these alterations is questionable, these methods are usually used in dry eye patients only as a last resort.

It has also been suggested to administer orally a dilute solution of pilocarpine to stimulate the autonomic nervous system to effect increased aqueous tear production. This method of treatment has not met with universal favor because of the unpleasant side effects suggested pilocarpine.

Animal models of Sjogren's syndrome have instrumental in basic ophthalmic research. A Sjogre like disease has been found in dogs with systemic lu erythematosus.

Canine KCS is a common, chronic progressive, an potentially blinding disease. A continuum of cornea and conjunctival lesions ensues from the dry eye state The cause of KCS in canines is often not identified Usually, canine KCS is not an isolated ophthalmic dis ease. It has been speculated in Kaswan et al., Am. J Vet. Res. 46, 376–383 (1985), that most cases of canin KCS occur via autoimmune mechanisms.

The term autoimmunity is used to indicate immunc logic self injury, but not a singular etiology. Autoim

mune disease is multifactorial, including hormonal, environmental, and polygenetic factors. A reasonable concept of autoimmune pathogenesis proposes that autoimmunity may arise whenever there exists a state of immunologic imbalance in which B-cell activity is excessive and/or suppressor T-cell activity is diminished.

Cyclosporins are unique immunosuppressive agents derived from an extract of soil fungi. Cyclosporine (Cyclosporin A) and its natural and synthetic analogs and isomers (such as Cyclosporins B, C, D, E and H) are cyclic peptides composed of 11 amino acid residues. Wenger, *Synthesis of Cyclosporine and Analogues*, pp. 14–25 in *Cyclosporine* vol. 1, Grune & Stratton, Inc. (New York 1983). Cyclosporin A was first proposed for use as an antifungal agent, but its immunosuppressive effects were found to be more marked than its antifungal potential. This drug inhibits the generation of effector T-lymphocytes without inhibiting the expression of suppressor lymphocytes.

Cyclosporine's immunosuppressive properties have led to its use in immune system related diseases. For example, U.S. Pat. No. 4,649,047, the disclosure of which is herein incorporated by reference, describes a method for the treatment of phacoanaphylactic endophthalmitis and uveitis in the anterior or posterior segment of an eye, in which method a cyclosporin is topically administered to the eye. In other ophthalmic applications, cyclosporine has been used topically only for the treatment of external (e.g., corneal) eye diseases.

BenEzra et al., Amer. J. Ophthalmol. 101, 278–282 (1986), describe the effect of 2% cyclosporine eyedrops on severe vernal keratoconjunctivitis. Severe vernal keratoconjunctivitis is a seasonal allergic disorder unrelated to tear deficiency.

Hunter et al., Clin. Exp. Immunol. 45, 173–177 (1981) describe the topical administration of cyclosporine in a rabbit model of corneal graft rejection with positive results. These effects were found to be attributable to T-cell suppression within the eye or within systemic compartments such as blood or lymph.

Boisjoly et al., Arch. Ophthalmol. 102, 1804–1807, (1984), have reported that topical application of cyclosporine had a beneficial prophylactic effect towards the treatment of severe herpetic stromal keratitis.

Mosteller et al., Investigative Ophthalmol. Supp. 25, 3, 38 (1984), propose the potential suppression of deleterious ocular immune reactions such as the eye surface cornea allograft reaction by applying a single dose of a 10% Cyclosporin A ointment in the lower cul-de-sac of rabbit eyelids.

In other ophthalmic applications, where the disease being treated is not limited to the eye surface, cyclosporine has been used systemically.

For example, Nussenblatt et al., Amer. J. Ophthalmol. 96, 275–282 (1983), have reported clinical improvement in some patients with noninfectious posterior uveitis following systemic treatment with cyclosporin.

However, systemic therapy with cyclosporine has serious drawbacks. There is a high risk of adverse responses when cyclosporine is used systemically. Cyclosporine used systemically has been associated with a high incidence of renal toxicity (kidney failure), some cases of hepatotoxicity, increased incidence of lymphoid tumors and increased incidence of opportunistic infections. Cyclosporine is only slightly less toxic than other immunosuppressive agents such as cytoxan or aziothioprine. The systemic side effects of cyclosporine are so severe and so common that they limit its use to life-threatening or in some cases severe sight-threatening disease. Finally, systemic application of cyclosporine is limited by its prohibitive cost.

To date, there has been no suggestion to treat a glandular dysfunction, a lacrimal gland dysfunction or an aqueous-deficient dry eye state with a cyclosporin, either topically or systemically.

It can thus be readily appreciated that provision of a method of increasing tear production in a patient suffering from deficient tears in the eye due to an autoimmune dysfunction of the lacrimal glands, which method provides improved treatment of KCS and eliminate previously discussed problems, would be a highly desirable advance over the current state of the art in KCS treatment.

## OBJECTS OF THE INVENTION

It is therefore an object of this invention to provide a method of increasing tear production for a tear-deficient eye.

It is a second object of this invention to provide a method of increasing tear production in an eye of a patient suffering from an immune mediated dysfunction of the lacrimal glands.

It is an additional object of this invention to provide a method of treating KCS in a patient suffering therefrom.

It is also an object of this invention to provide a method of treating a disorder caused by excessive immune activity in a lacrimal gland of a patient.

It is a further object of this invention to provide a method of treating a disorder exacerbated by KCS in a patient suffering therefrom.

It is another object of this invention to provide a cyclosporin-based treatment of the lacrimal glands without the accompanying adverse physiological responses and economic difficulties associated with systemic cyclosporin treatments.

These and other objects and advantages of the present invention will become more readily apparent after consideration of the following.

## STATEMENT OF THE INVENTION

In one aspect, the present invention is directed to a method of treating a dry eye state in a patient by administering a cyclosporin topically to the patient's eye.

In another of its aspects, the present invention provides a cyclosporin-based treatment of an autoimmune dysfunction of the lacrimal glands.

In still another of its aspects, the present invention relates to a cyclosporin in a carrier adaptable to topical administration into a patient's eye.

## DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention, as well as other objects and features thereof, will be understood more clearly and fully from the following description of certain preferred embodiments.

The present invention provides a method of treating an aqueous-deficient dry eye state due to an autoimmune dysfunction of the lacrimal glands in a patient suffering therefrom, which method includes the step of administering a cyclosporin topically to the patient's eye. Surprisingly, this topical administration of a cyclosporin to the eye provides cyclosporin treatment to

the lacrimal glands, and such treatment increases tear production in a patient suffering from KCS.

Conventional treatment of KCS involves alleviating the symptoms of the dry eye state without treating the underlying disorders or causes of the dry eye state. Symptomatic treatment of the dry eye state, such as by supplementation of the aqueous tears with artificial tear substitutes, necessarily involves continuous and repeated attention as needed to alleviate the recurring symptoms.

To date, there has been no suggestion to treat a glandular dysfunction, a lacrimal gland dysfunction or an aqueous-deficient dry eye state with a cyclosporin, either topically or systemically.

Topical administration to a patient's eye has surprisingly been found to be an excellent method for providing a cyclosporin to the lacrimal glands of the patient to treat KCS. Additionally, since by its very nature topical administration does not require cyclosporin dispersion throughout the patient's system as is the case with systemic administrations, the present invention provides a means for directing cyclosporin to the desired location without the accompanying high risk of adverse responses and high cost associated with systemic treatments.

Cyclosporine concentration was determined for various eye compartments and tissues surrounding the eye after bilateral topical administration of cyclosporine to the eyes of three rabbits. The cyclosporine was administered in each of the rabbits' eyes in drops (approximately 17 microliters) of 2% radiolabelled cyclosporine in an olive oil solution applied every 15 minutes for 6 applications, followed by a period of two hours to allow for absorption. The rabbits were then euthanized and the eyes and surrounding tissue were enucleated and frozen. The eyes and surrounding tissue were dissected into their component parts. These were then digested in collagenase and the resulting solutions were analyzed by liquid scintillation counting for cyclosporine content. The following average cyclosporine concentrations were measured:

Accessory lacrimal gland: 2850 mg of cyclosporine/-gram of tissue;
Periorbital fat: 800 ng/gram;
Cornea: 4700 ng/gram;
Iris: 1200 ng/gram;
Retina: 50 ng/gram;
Aqueous humor: 30 ng/gram;
Vitreous humor: 30 ng/gram;
Anterior sclera: 3150 ng/gram; and
Posterior sclera: 1550 ng/gram.

Thus, topical administration of cyclosporine to a patient's eye surprisingly provides a suitable concentration of cyclosporine to the lacrimal glands of the patient for treatment of KCS.

In accordance with the present invention, the cyclosporin may be used in any efficacious concentration, e.g., 0.01 to saturation (e.g., greater than 20 weight percent), in a pharmaceutically acceptable excipient. From 0.01 to 50 weight percent, preferably from 0.1 to 20 weight percent, of a cyclosporin in a pharmaceutically acceptable excipient is used. Such pharmaceutically acceptable excipients are, 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.

Examples of these pharmaceutically acceptable excipients are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, chremophor, Miglyol 182 (commercially available from Dynamit Nobel Kay-Fries Chemical Company, Mont Vale, N.J.), an alcohol (e.g., ethanol, n-propyl alcohol or iso-propyl alcohol), liposomes or liposome-like products or a silicone fluid. Preferred excipients are dimethyl sulphoxide and olive oil. Mixtures of at least two of any suitable excipients may be used.

Examples of artificial tear excipients which can be advantageously used in the practice of this invention are isotonic sodium chloride, cellulose ethers such as hydroxypropylmethylcellulose and hydroxyethylcellulose, polyvinyl alcohol and other commercially available artificial tea solutions.

An example of useful polymeric excipient is a polyoxyethylated castor oil.

Examples of pharmaceutically acceptable membranes which can advantageously be used in the practice of this invention are: microdone, an artificial lipid membrane, polyvinylalcohol, or methylcellulose.

The cyclosporin is advantageously administered topically as an ophthalmic drop (solution or suspension) or ophthalmic ointment containing a effective amount of the cyclosporin. Concentrations of 0.01 to 50 weight percent, preferably 0.1 to 20 weight percent, of a cyclosporin are used.

In accordance with the method of the present invention, a cyclosporin is administered topically in any quantity required to provide the degree of treatment needed. For example, 5 microliters to 1 milliliter of a solution, suspension or ointment containing an effective amount of a cyclosporin, such as 0.01 to 50 weight percent, preferably 0.1 to 20 weight percent, of cyclosporin is advantageously used.

Cyclosporins which are useful in the practice of the present invention are both natural or synthetic cyclosporin. For example, Cyclosporin A is advantageously used in the practice of the present invention. Other forms of cyclosporins (e.g., analogs and isomers such as Cyclosporins B, C, D, E, and H) may also be used. Mixtures of at least two different cyclosporins may be used.

Numerous advantages accrue with the practice of the present invention. The method of the present invention is useful in that it can locally prevent activation of a presystemic response. Topical administration of a cyclosporin into a patient's tear deficient eye increases tear production in the eye. Thus, such treatment further serves to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea. Furthermore, cyclosporin directly decreases the immune response of granulation and neovascularization in the cornea.

Further objects of this invention, together with additional features contributing thereto and advantages accruing therefrom, will be apparent from the following examples of the invention.

## EXAMPLE 1

A one year old standard female Poodle with conjunctivitis exhibited mild aqueous tear deficiency in both eyes. The dog had a Schirmer tear test value of 15 mm/minute in the right eye and 10 mm/minute in the left eye.

The Schirmer tear test is a test of aqueous tear production. The test depends upon observing the extent of wetting of a strip of filter paper placed over the lower lid of an eye for a specified time. Standardized strips are commercially available. The strip is folded at a notched marking and is then placed over the edge of the lateral one-third of the eyelid. The strip is usually left in place for a period of time while the patient looks straight ahead in dim light.

The degree of wetting of the paper is measured in mm from the notch. For human patients, a normal end point is 5 mm of wetting at five minutes. For canine patients, the normal tear production is 14 to 20 mm. of wetting at one minute.

The dog was treated with dexamethasone by topical administration in both eyes four times daily.

The same dog at approximately six years old still exhibited conjunctivitis in both eyes and had a Schirmer tear test value of 3 mm/minute in both eyes. Topical dexamethasone was used in both eyes twice daily for nine weeks without benefit.

The dog was then treated by topical application of 2% cyclosporine in an olive oil solution in both eyes once daily without any other medications. After ten days, the dog showed markedly increased tear production and had a Schirmer tear test value of 22 mm/minute in the right eye and 8 mm/minute in the left eye.

The treatment by topical application of 2% cyclosporine in an olive oil solution in both eyes once daily was continued for an additional three weeks. At this time, the dog exhibited plentiful aqueous tear production and the treatment was stopped for one week. After this week, the dog had a Schirmer tear test value of 10 mm/minute in the right eye and 9 mm/minute in the left eye.

At this time, the treatment by topical application of 2% cyclosporine in an olive oil solution in both eyes once daily was restarted and continued for six days. After these six days, the dog had a Schirmer tear test value of 22 mm/minute in the right eye and 16 mm/minute in the left eye.

In this case, a dog with chronic tear deficiency in which prior use of corticosteroids failed to improve tear secretion showed a surprising increase in tear production with cyclosporine treatment. The increased tear production continued only while cyclosporine therapy continued. When the treatment was stopped for a week, recurrence of tear deficiency was found. However, tear production increased to normal levels after the treatment was restarted.

## EXAMPLE 2

An eight year old male Lhasa Apso had had a four year prior cat scratch in his left eye and an active 4 mm stromal ulcer in his right eye. An ocular examination of the dog showed conjunctivitis in both eyes with mucopurulent discharge, diffuse irregular corneal surfaces, pigment formation and neovascularization in the cornea of the left eye. The Schirmer tear test values were 12 mm/minute in the right eye and 3 mm/minute in the left eye.

The dog was treated with topical administration to both eyes of 2% cyclosporine in an olive oil solution once daily, neosporin twice daily and ophthalmic petrolatum. After five days, the Schirmer tear test values were 22 mm/minute in the right eye and 23 mm/minute in the left eye. In addition, the ulcer in the right eye was healed to 2 mm and the left eye was assessed to have decreased vascularization.

In this case, cyclosporine increased tear production significantly in a short period of time. Moreover, cyclosporine, unlike corticosteroids, did not retard corneal healing nor activate corneal collagenase. Accordingly, cyclosporine can be used in eyes having active corneal ulcers.

## EXAMPLE 3

A six year old male English Bulldog had had a long history of KCS. The Schirmer tear test values were 2 mm/minute in the right eye and 3 mm/minute in the left eye.

The right eye was neovascularized over the entire cornea. No intraocular detail could be visualized through the opaque cornea. The cornea was grossly thick and irregular in surface. The left eye had neovascularization over about half of the cornea, mostly axially.

The dog was treated with three drops of 2% pilocarpine by mouth. After two hours, the Schirmer tear test values were 0 mm/minute in the right eye and 10 mm/minute in the left eye.

The dog was then treated with 2% cyclosporine in an olive oil solution administered topically to both eyes once daily and three drops of 2% pilocarpine administered by mouth twice daily. After twelve days, the Schirmer tear test values were 10 mm/minute in the right eye and 15 mm/minute in the left eye.

In this case, while pilocarpine alone increased tear production in the left eye from a Schirmer tear test value of 3 mm/minute to 10 mm/minute, pilocarpine did not increase tear production in the right eye. Use of cyclosporine with pilocarpine increased tear production to a Schirmer tear test value of 15 mm/minute in the left eye and from 0 mm/minute to 10 mm/minute in the right eye. The use of cyclosporine markedly increased tear production over the use of pilocarpine alone.

## EXAMPLE 4

A seven year old Miniature Poodle had a history of severe KCS of six to seven months duration. The dog was considered to be blind for two months duration. Treatment with artificial tears six times daily did not effect the apparent blindness.

The dog showed marked mucopurulent discharge in both eyes. The Schirmer tear test values were 0 mm/minute in both eyes. The dog's corneas were thickened and neovascularized with an irregular surface. No intraocular detail could be visualized through the opaque corneas.

The dog was treated with one drop of 2% pilocarpine by mouth two times daily and ophthalmic petrolatum four times daily. After two weeks, the Schirmer tear test values were still 0 mm/minute in both eyes. The corneal vascularity and scarring remained dense and the anterior chambers of the dog's eye were not visualizable.

The dog was then treated with 2% cyclosporine in an olive oil solution administered topically in both eyes once daily and two drops pilocarpine administered by mouth twice daily.

After two weeks, the Schirmer tear test values were 8 mm/minute in the right eye and 6 mm/minute in the left eye. Although corneal vascularization and scarring remained, the iris and lens could be evaluated, there was

no mucoid discharge in either eye as previously and the KCS was assessed as medically improved.

After similar treatment for another two months, the Schirmer tear test values were 11 mm/minute in the right eye and 17 mm/minute in the left eye. The dog's eyes had minimal corneal vascularization and minimal scarring.

In this case, although the dog was treated initially with pilocarpine, pilocarpine alone is not known to cause such a drastic improvement in tear production. After treatment with cyclosporine, the dog improved from no tear flow in either eye to normal tear production in both eyes. The dog improved from blinding corneal inflammation to very mild corneal pigmentation in both eyes. Treatment with cyclosporine markedly increased tear production and allowed the dog to return to normal vision.

I claim:

1. A method for enhancing or restoring lacrimal gland tearing comprising topically administering cyclosporin to the eye in a pharmaceutically acceptable vehicle.

2. The method of claim 1 for increasing tear production in a tear-deficient eye comprising topically administering a therapeutically effective amount of a cyclosporin to said eye.

3. The method of claim 2 wherein said cyclosporin is administered as a solution, suspension or ointment comprising 0.01 to 50 weight percent of cyclosporin in a pharmaceutically acceptable excipient.

4. The method of claim 3 wherein said cyclosporin is administered in an amount of 0.1 to 20 weight percent.

5. The method of claim 3 wherein the pharmaceutically acceptable excipient is olive oil, arachis oil, castor oil, polyoxyethylated castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol, liposome, silicone fluid or a mixture thereof.

6. The method of claim 2, wherein said cyclosporin is Cyclosporin A.

7. The method of claim 2 for increasing tear production in an eye of a patient suffering from an autoimmune dysfunction of the lacrimal glands comprising administering a therapeutically effective amount of a cyclosporin topically to the patient's eye.

8. The method of claim 2 for treating keratoconjunctivitis sicca in a patient comprising the step of administering a therapeutically effective amount of a cyclosporin topically to the patient's eye.

9. The method of claim 1 for treating a disorder caused by immune activity in a lacrimal gland of a patient comprising the step of topically administering to the patient's eye a therapeutically effective amount of a cyclosporin to enhance or restore tearing.

10. The method of claim 9 wherein said cyclosporin is administered as a solution, suspension or ointment comprising 0.01 to 50 weight percent of cyclosporin in a pharmaceutically acceptable excipient.

11. The method of claim 10 wherein said cyclosporin is administered in an amount of 0.1 to 20 weight percent.

12. The method of claim 10 wherein the pharmaceutically acceptable excipient is olive oil, arachis oil, castor oil, polyoxyethylated castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol, liposome, silicone fluid or a mixture thereof.

13. The method of claim 9, wherein said cyclosporin is Cyclosporin A.

14. The method of claim 1 for treating a disorder exacerbated by deficient tear production in a patient comprising topically administering a therapeutically effective amount of a cyclosporin to the patient's eye to enhance or restore tearing.

15. The method of claim 14 wherein said cyclosporin is administered as a solution, suspension or ointment comprising 0.01 to 50 weight percent of cyclosporin in a pharmaceutically acceptable excipient.

16. The method of claim 15 wherein said cyclosporin is administered in an amount of 0.1 to 20 weight percent.

17. The method of claim 15 wherein the pharmaceutically acceptable excipient is olive oil, arachis oil, castor oil, polyoxyethylated castor oil, mineral oil, petroleum jelly, dimethyl sulphoxide, an alcohol, liposome, silicone fluid or a mixture thereof.

18. The method of claim 14, wherein said cyclosporin is Cyclosporin A.

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# United States Patent [19]

Ding et al.

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[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.

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[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

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*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 preferably, the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5, and the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.

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

## DETAILED DESCRIPTION

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

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

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

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

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

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



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

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

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

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

Example 1

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

Example 2

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

Example 3

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

Example 4

| | A |
|---|---|
| Castor oil | 5.00% |

-continued

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

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

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

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

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

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

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

What is claimed is:

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

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

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

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

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

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

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

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

* * * * *

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

## 1.5 CERTIFICATION FOR EXCLUSIVITY

Allergan, Inc. (the applicant) is submitting information in support of a request for five-year exclusivity per Sections 505(c)(3)(D) and 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act for NDA 21-023 Cyclosporine Ophthalmic Emulsion. The results of the following two controlled clinical studies demonstrated that Cyclosporine Ophthalmic Emulsion is safe and efficacious for the treatment of the signs and symptoms of moderate to severe keratoconjunctivitis sicca (KCS) with or without Sjögren's Syndrome. In the applicant's opinion these studies are essential to the approval of the new drug application for Cyclosporine Ophthalmic Emulsion. The applicant was the sponsor of IND 32,133 under which these clinical studies were conducted:

192371-002

A Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine 0.05% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up To One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca

192371-003

A Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine 0.05% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up To One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca

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2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

Allergan, Inc. hereby certifies that to the best of our knowledge, the clinical investigations listed herein have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application or supplement. Furthermore, no other drug product containing all of the same ingredients with the same conditions of approval has been previously approved for human use. The scientific literature has been thoroughly searched and in the applicant's opinion there are no published studies or publicly available reports of clinical investigations (other than those sponsored by the applicant) to support the approval of the new drug application for Cyclosporine Ophthalmic Emulsion. The applicant is not aware of any approvals of this product for human use.

Peter A. Kresel, MS, MBA (Date)

Sr. Vice President, Global Regulatory Affairs

Allergan, Inc.