

**NDA 21-023**

**Cyclosporine Ophthalmic Emulsion, 0.05%**

**Original NDA Filing**

**February 24, 1999**

**Volume 1 of 171**



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



**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  
Director  
Regulatory Affairs

EB/mkb



March 1, 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

DESK COPY

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  
Director  
Regulatory Affairs





**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  
February 24, 1999

Pre-submission of CMC  
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



**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



**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  
Director  
Regulatory Affairs

Enclosure (2 boxes)

EB/mkb



**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

# 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  
Director  
Regulatory Affairs



February 17, 1999

U. S. Food and Drug Administration  
C/O Mellon Bank  
Three Mellon Bank Center  
27<sup>th</sup> 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  
Director, Regulatory Affairs

EB/dmo  
Enclosure: Check Number 103765



Account with Vendor  
Account at Vendor

1000003970

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 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



Check Number **103765**  
66-763 531  
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⑈



# CHECK REQUEST

**INVOICE # CKRQ****ACCOUNTS PAYABLE USE ONLY**

CHECK APPROPRIATE BOX:

<input type="checkbox"/> AGN, INC - 0010	<input type="checkbox"/> SURGICAL - 0110	<input type="checkbox"/> AGN SALES - 0120	<input type="checkbox"/> AGN AMERICA	<input type="checkbox"/> HATO REY, PUERTO RICO
<input type="checkbox"/> VPLP - 0040	<input type="checkbox"/> OMS - 0150	<input type="checkbox"/> AMO (PUERTO RICO)	<input type="checkbox"/> OTHER	
<input type="checkbox"/> WACO - 0050	<input checked="" type="checkbox"/> AGN SERVICES - 0170	<input type="checkbox"/> CANADA		

MAKE CHECK PAYABLE TO: <b>U. S. Food and Drug Administration</b>	VENDOR #: (IF KNOWN)	DATE: <b>1/21/99</b>
---	----------------------	-------------------------

ADDRESS: <b>Mellon Bank (FDA 360909) Three Mellon Bank Center, 27th Floor</b>	SOCIAL SECURITY #: REQUIRED FOR NEW VENDORS - -
CITY/STATE/PROVINCE/COUNTRY: ZIP CODE: <b>Pittsburgh, PA 15259-0001</b>	OR Tax I.D. # - -
INTERNAL ORDER #:	CDN \$ <input type="checkbox"/> U.S. \$ <input type="checkbox"/> OTHER <input type="checkbox"/>

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
<i>(FOR CANADIAN USE ONLY)</i>						
GST	001	1	2120	00	060 51	
GST	001	1	2120	00	030 09	
CHECK TOTAL						\$272,282.00

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

APPROVED SIGNATURE MUST APPEAR ON "AUTHORIZED SIGNATURE LIST"

APPROVED BY (PLEASE PRINT): <b>Peter Kresel, Sr. VP</b>	(SIGNATURE) 	YOUR \$ LIMIT: <b>\$1 million</b>	DATE: <b>1/26/99</b>
--	-----------------	--------------------------------------	-------------------------

NOTE: INSTRUCTIONS TO PREPARER

- FILL OUT THE CHECK REQUEST FORM COMPLETELY. INCOMPLETE FORMS WILL BE RETURNED.
- ATTACH SUPPORTING DOCUMENTATION. WITHOUT DOCUMENTATION, THIS FORM WILL BE RETURNED.
- PLEASE DO NOT USE THIS FORM FOR THE FOLLOWING:
  - \* EMPLOYEE REIMBURSEMENT OF ANY KIND
  - \* IN LIEU OF A VENDOR INVOICE
  - \* IN LIEU OF AN INVOICE PAID AGAINST A P.O.
  - \* IT IS NOT NECESSARY TO ATTACH A CHECK REQUEST TO AN APPROVED INVOICE

CHECK NEEDED BY:  
**4-Feb-99**

SPECIAL MAILING INSTRUCTIONS:

**PLEASE CALL DONNA ODDY FOR PICK-UP X 6824. DO NOT MAIL**

NAME: <b>Elizabeth Bancroft</b>	EXT.:# <b>4391</b>	MAIL CODE: <b>LS-1F</b>
C.C.:		



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.

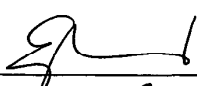

If checks are to be sent by a courier that requests a street address, they can be sent to: Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001. (Note: This Mellon Bank Address is for courier delivery only.) Please make sure that the FDA P.O. Box number (P.O. Box 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 RA Director		1/25/99	
Peter Kresel Sr. VP Global RegAff		2/4/99	
Bob Koda RA Consultant	N/A		

<b>PRODUCT:</b>	Cyclosporine Ophthalmic Emulsion		
<b>PROJECT:</b>	NDA Sections 1 through 3		
<b>COUNTRY:</b>	USA		
<b>ANALYST:</b>	Mari Bradford (X4392)	<b>DATE ROUTED:</b>	
<b>DATE MAILED:</b>			

<b>Volume 1 Table of Contents</b>	<b>Vol.</b>	<b>Page</b>
Section 1 INDEX AND CERTIFICATIONS .....	1	002
Form FDA 356h .....	1	002
Form FDA 3397 .....	1	005
COVER LETTER .....	1	007
1.1 MASTER INDEX .....	1	102
1.2 LIST OF PRIOR RELATED SUBMISSIONS .....	1	102
Letter August 26, 1996 .....	1	103
Letter December 9, 1996 .....	1	105
Letter May 21, 1997 .....	1	108
Letter January 12, 1998 .....	1	111
Teleconference June 25, 1998 .....	1	112
Letter December 7, 1998 .....	1	114
Letter December 9, 1998 .....	1	116
1.3 DMF REFERENCES .....	1	118
Novartis Authorization Letter 1998 .....	1	119
Allergan Waco .....	1	121
Chevron .....	1	122
1.4 PATENT INFORMATION .....	1	123
Patent 4,649,047 .....	1	124
Patent 4,839,342 .....	1	134
Patent 5,474,979 .....	1	140
1.5 CERTIFICATION FOR EXCLUSIVITY .....	1	144
1.6 DEBARMENT CERTIFICATION .....	1	146
1.7 FIELD COPY CERTIFICATION .....	1	147
1.8 FINANCIAL CERTIFICATION .....	1	148
1.9 NOTES TO REVIEWER AND ERRATA .....	1	156
1.9.1 NOTES TO REVIEWER .....	1	156
Electronic Copy of the NDA .....	1	156
Color Copies of Photographs .....	1	156
1.9.2 ERRATA .....	1	157
Section 2 LABELING .....	1	159
2.1 ANNOTATED LABELING .....	1	159
2.2 DRAFT LABELING .....	1	175
Section 3 SUMMARY .....	1	192

3.1 PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE, INTENDED USE, AND POTENTIAL CLINICAL BENEFITS . . . . .	1	192
3.1.1 PHARMACOLOGIC CLASS . . . . .	1	192
3.1.2 SCIENTIFIC RATIONALE . . . . .	1	192
3.1.3 INTENDED USE . . . . .	1	194
3.1.4 POTENTIAL CLINICAL BENEFITS . . . . .	1	195
3.1.5 REFERENCES . . . . .	1	197
3.1.5.1 Study Report References . . . . .	1	197
3.1.5.2 Literature References . . . . .	1	199
3.2 FOREIGN MARKETING HISTORY . . . . .	1	202
3.2.1 COUNTRIES WHERE THE DRUG HAS BEEN MARKETED. . . . .	1	202
3.2.2 COUNTRIES WHERE THE DRUG HAS BEEN WITHDRAWN FROM MARKETING. . . . .	1	202
3.2.3 COUNTRIES WHERE MARKETING APPLICATIONS ARE PENDING . . . . .	1	202
3.3 CHEMISTRY, MANUFACTURING AND CONTROLS SUMMARY 1		203
3.3.1 ACTIVE PHARMCEUTICAL INGREDIENT . . . . .	1	204
3.3.2 DRUG PRODUCT . . . . .	1	204
3.3.2.1 Quantitative Composition . . . . .	1	204
3.3.2.2 Container-Closure System. . . . .	1	205
3.3.2.2.1 Schematic . . . . .	1	206
3.3.2.2.1 Qualification of Container and Closures . . . . .	1	208
3.3.2.3 Product Tests, Specifications, and Analytical Methods . . . . .	1	210
3.3.2.3.1 Rationale for Drug Product Specifications: . . . . .	1	211
3.3.2.3.2 Rationale for Analytical Tests for Drug Product: . . . . .	1	212
3.3.2.3.3 Stability. . . . .	1	216
3.3.6 CORRELATION OF DRUG SUBSTANCE LOTS USED IN CLINICAL, TOXICOLOGY, AND PRODUCT STABILITY LOTS . . . . .	1	216
Table 3.3.6-1 Active Pharmaceutical Ingredient Lots Used in Clinical and Non-Clinical Studies . . . . .	1	217
Table 3.3.6-2 Formulations Used in Non-Clinical Studies . . . . .	1	222
3.4 NONCLINICAL SUMMARY . . . . .	1	223
3.4.1 PHARMACOLOGY . . . . .	1	223
3.4.2 TOXICOLOGY . . . . .	1	224
3.4.3 PHARMACOKINETICS . . . . .	1	225
3.5 CLINICAL PHARMACOKINETICS SUMMARY. . . . .	1	226



3.5.1 SYSTEMIC EXPOSURE AFTER OPHTHALMIC ADMINISTRATION. . . . .	1	226
Table 3.5.1-1. Comparison of dose and subsequent mean blood Cmax, Coverage, Cmin, and AUC0-12 between systemic therapeutic use of NEORAL® and topical use of 0.05% and 0.1% cyclosporine emulsions. . . . .	1	227
3.5.2 OCULAR PHARMACOKINETICS AFTER OPHTHALMIC ADMINISTRATION. . . . .	1	227
3.6 MICROBIOLOGY SUMMARY . . . . .	1	228
3.7 CLINICAL SUMMARY. . . . .	1	229
3.7.1 CLINICAL PHARMACOLOGY AND PHARMACOKINETICS	1	229
3.7.1.1 Background . . . . .	1	229
3.7.1.2 Assessment of Immune Activation and Inflammatory Response. . . . .	1	229
3.7.1.3 Ocular Surface Inflammation. . . . .	1	230
3.7.1.4 Pharmacologic Activity . . . . .	1	231
3.7.1.5 Conclusions . . . . .	1	233
3.7.1.6 References . . . . .	1	233
3.7.2 OVERVIEW OF CLINICAL STUDIES. . . . .	1	236
3.7.2.1 Introduction . . . . .	1	236
3.7.2.2 Design of the Phase 3 Clinical Trials . . . . .	1	236
3.7.2.3 FDA/Sponsor Discussions. . . . .	1	240
3.7.2.5 References . . . . .	1	242
3.7.3 CONTROLLED CLINICAL STUDIES . . . . .	1	243
3.7.3.1 Introduction . . . . .	1	243
3.7.3.2 Tabular Presentation of Studies. . . . .	1	243
3.7.3.3 Phase 2 Dose-Response Study. . . . .	1	247
3.7.3.4 Phase 3 Study Design . . . . .	1	252
3.7.3.5 Phase 3 Patient Disposition and Demographics . . . . .	1	254
3.7.3.6 Phase 3 Intent-to-Treat Analysis of Efficacy Results . . . . .	1	255
3.7.3.7 Results of Phase 3 Tertiary Ophthalmic Tests. . . . .	1	263
3.7.3.8 Phase 3 Pharmacokinetics Results. . . . .	1	267
3.7.3.9 Phase 3 Safety Results. . . . .	1	267
3.7.3.10 Dose and Regimen Rationale. . . . .	1	270
3.7.3.11 Discussion . . . . .	1	271
3.7.3.12 Conclusions . . . . .	1	275
3.7.3.13 References . . . . .	1	277

3.7.4 OTHER STUDIES AND INFORMATION . . . . .	1	281
3.7.5 SAFETY SUMMARY GENERAL SAFETY CONCLUSIONS . .	1	282
3.7.5.1 Extent of Exposure . . . . .	1	282
3.7.5.2 Demographics and Other Patient Characteristics . . . . .	1	284
3.7.5.3 Adverse Events . . . . .	1	284
3.7.5.4 Laboratory Data . . . . .	1	290
3.7.5.5 Other Safety Assessments . . . . .	1	291
3.7.5.6 Drug-Drug Interactions . . . . .	1	292
3.7.5.7 Drug Abuse and Overdosage . . . . .	1	293
3.7.5.8 Safety Information from Other Sources . . . . .	1	293
3.7.5.9 Discussion . . . . .	1	294
3.7.5.10 Conclusions . . . . .	1	297
3.7.5.11 References . . . . .	1	298
3.8 DISCUSSION OF THE BENEFIT/RISK RELATIONSHIP AND PROPOSED ADDITIONAL STUDIES . . . . .	1	304
3.8.1 BENEFIT/RISK ASSESSMENT OF CYCLOSPORINE OPHTHALMIC EMULSION IN THE TREATMENT OF DRY EYE . .	1	304
3.8.1.1 Benefits . . . . .	1	304
3.8.1.2 Risks . . . . .	1	306
3.8.1.3 Conclusions . . . . .	1	308
3.8.2 PROPOSED POST-MARKETING CLINICAL STUDIES OR SURVEILLANCE . . . . .	1	309
3.8.3 REFERENCES . . . . .	1	310
3.8.3.1 Study Report References . . . . .	1	310
3.8.3.2 Literature References . . . . .	1	312



This application contains the following items: (Check all that apply)		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input checked="" type="checkbox"/>	4. Chemistry section	
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input checked="" type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
<input checked="" type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
<input checked="" type="checkbox"/>	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)	
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))	
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
	19. OTHER (Specify)	
<p><b>CERTIFICATION</b></p> <p>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:</p> <ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.</li> <li>5. Regulations on making changes in applications in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.</li> <li>6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>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.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p><b>Warning:</b> a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Elizabeth Bancroft</i>		TYPED NAME AND TITLE Elizabeth Bancroft, Director, Regulatory Affairs DATE 2/24/99
ADDRESS (Street, City State, and ZIP Code) 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534		Telephone Number (714) 246-4391
<p>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:</p> <p>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 <b>DO NOT RETURN</b> this form to this address.</p> <p>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.</p>		

FORM FDA 356h (4/97)

Continuation Sheet for

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

**ESTABLISHMENT INFORMATION FOR DRUG SUBSTANCE**

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

**ESTABLISHMENT INFORMATION FOR DRUG PRODUCT**

**Drug Product:** Cyclosporine Ophthalmic Emulsion, 0.05% and 0.1%  
**Application Number:** NDA 21-023

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

Public reporting burden for this collection of information is estimated to average 30 minutes 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 (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
2000 Independence Avenue, S.W.  
Washington, DC 20201

"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 number."

*See Instructions on Reverse Before Completing This Form.*

<b>1. APPLICANT'S NAME AND ADDRESS</b>  Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534	<b>2. USER FEE BILLING NAME, ADDRESS AND CONTACT</b>  Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534  Contact: Elizabeth Bancroft
<b>3. TELEPHONE NUMBER (Include Area Code)</b> 800-347-4500	
<b>4. PRODUCT NAME</b> Cyclosporine Ophthalmic Emulsion, 0.05%	
<b>5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM	
<b>6. USER FEE I.D. NUMBER</b> 3632	<b>7. LICENSE NUMBER/NDA NUMBER</b>  N021023
<b>8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</b>	
<input type="checkbox"/> <b>A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92</b> <input type="checkbox"/> <b>THE APPLICATION IS SUBMITTED UNDER 505(b)(2)</b> <small>(See reverse before checking box.)</small>	
<input type="checkbox"/> <b>AN INSULIN PRODUCT SUBMITTED UNDER 506</b>	
FOR BIOLOGICAL PRODUCTS ONLY	
<input type="checkbox"/> <b>WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION</b> <input type="checkbox"/> <b>A CRUDE ALLERGENIC EXTRACT PRODUCT</b>	
<input type="checkbox"/> <b>BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92</b> <input type="checkbox"/> <b>AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT</b>	
<b>9.a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?</b> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <small>(See reverse if answered YES)</small>	
<b>b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?</b> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <small>(See reverse if answered YES)</small>	
<b><i>This completed form must be signed and accompany each new drug or biologic product, original or supplement.</i></b>	

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

*Elizabeth Bancroft*

TITLE

Elizabeth Bancroft  
Director, Regulatory Affairs

DATE

*2/24/99*

**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



**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

Original NDA Filing  
NDA 21-023  
Page 3

(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  
Director  
Regulatory Affairs

EB/mkb

<b>Section 1</b>	<b>Vol.</b>	<b>Page</b>
Section 1 INDEX AND CERTIFICATIONS .....	1	002
Form FDA 356h .....	1	002
Form FDA 3397 .....	1	005
COVER LETTER .....	1	007
1.1 MASTER INDEX .....	1	102
1.2 LIST OF PRIOR RELATED SUBMISSIONS .....	1	102
Letter August 26, 1996 .....	1	103
Letter December 9, 1996 .....	1	105
Letter May 21, 1997 .....	1	108
Letter January 12, 1998 .....	1	111
Teleconference June 25, 1998 .....	1	112
Letter December 7, 1998 .....	1	114
Letter December 9, 1998 .....	1	116
1.3 DMF REFERENCES .....	1	118
Novartis Authorization Letter 1998 .....	1	119
Allergan Waco .....	1	121
Chevron .....	1	122
1.4 PATENT INFORMATION .....	1	123
Patent 4,649,047 .....	1	124
Patent 4,839,342 .....	1	134
Patent 5,474,979 .....	1	140
1.5 CERTIFICATION FOR EXCLUSIVITY .....	1	144
1.6 DEBARMENT CERTIFICATION .....	1	146
1.7 FIELD COPY CERTIFICATION .....	1	147
1.8 FINANCIAL CERTIFICATION .....	1	148
1.9 NOTES TO REVIEWER AND ERRATA .....	1	156
1.9.1 NOTES TO REVIEWER .....	1	156
Electronic Copy of the NDA .....	1	156
Color Copies of Photographs .....	1	156
1.9.2 ERRATA .....	1	157



1.1 MASTER INDEX		Vol.	Page
<b>Section 1 INDEX AND CERTIFICATIONS.....</b>	<b>1</b>	<b>002</b>	
Form FDA 356h .....	1	002	
Form FDA 3397 .....	1	005	
COVER LETTER .....	1	007	
1.1 MASTER INDEX .....	1	102	
1.2 LIST OF PRIOR RELATED SUBMISSIONS .....	1	102	
Letter August 26, 1996 .....	1	103	
Letter December 9, 1996 .....	1	105	
Letter May 21, 1997 .....	1	108	
Letter January 12, 1998 .....	1	111	
Teleconference June 25, 1998 .....	1	112	
Letter December 7, 1998 .....	1	114	
Letter December 9, 1998 .....	1	116	
1.3 DMF REFERENCES .....	1	118	
Novartis Authorization Letter 1998 .....	1	119	
Allergan Waco .....	1	121	
Chevron .....	1	122	
1.4 PATENT INFORMATION .....	1	123	
Patent 4,649,047 .....	1	124	
Patent 4,839,342 .....	1	134	
Patent 5,474,979 .....	1	140	
1.5 CERTIFICATION FOR EXCLUSIVITY .....	1	144	
1.6 DEBARMENT CERTIFICATION .....	1	146	
1.7 FIELD COPY CERTIFICATION .....	1	147	
1.8 FINANCIAL CERTIFICATION .....	1	148	
1.9 NOTES TO REVIEWER AND ERRATA .....	1	156	
1.9.1 NOTES TO REVIEWER .....	1	156	
Electronic Copy of the NDA .....	1	156	
Color Copies of Photographs .....	1	156	
1.9.2 ERRATA .....	1	157	
<b>Section 2 LABELING .....</b>	<b>1</b>	<b>159</b>	
2.1 ANNOTATED LABELING .....	1	159	
2.2 DRAFT LABELING .....	1	175	
<b>Section 3 SUMMARY .....</b>	<b>1</b>	<b>192</b>	

3.1 PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE, INTENDED USE, AND POTENTIAL CLINICAL BENEFITS . . . . .	1	192
3.1.1 PHARMACOLOGIC CLASS . . . . .	1	192
3.1.2 SCIENTIFIC RATIONALE . . . . .	1	192
3.1.3 INTENDED USE . . . . .	1	194
3.1.4 POTENTIAL CLINICAL BENEFITS . . . . .	1	195
3.1.5 REFERENCES . . . . .	1	197
3.1.5.1 Study Report References . . . . .	1	197
3.1.5.2 Literature References . . . . .	1	199
3.2 FOREIGN MARKETING HISTORY . . . . .	1	202
3.2.1 COUNTRIES WHERE THE DRUG HAS BEEN MARKETED. . . . .	1	202
3.2.2 COUNTRIES WHERE THE DRUG HAS BEEN WITHDRAWN FROM MARKETING . . . . .	1	202
3.2.3 COUNTRIES WHERE MARKETING APPLICATIONS ARE PENDING . . . . .	1	202
3.3 CHEMISTRY, MANUFACTURING AND CONTROLS SUMMARY 1		203
3.3.1 ACTIVE PHARMCEUTICAL INGREDIENT . . . . .	1	204
3.3.2 DRUG PRODUCT . . . . .	1	204
3.3.2.1 Quantitative Composition . . . . .	1	204
Table 3.3.2.1-1 Quantitative Composition of Cyclosporine Ophthalmic Emulsion 0.05% (formula 9054X) . . . . .	1	205
Table 3.3.2.1-2 Quantitative Composition of Cyclosporine Ophthalmic Emulsion 0.1% (formula 8735X) . . . . .	1	205
3.3.2.2 Container-Closure System . . . . .	1	205
3.3.2.2.1 Schematic . . . . .	1	206
Figure 3.3.2.2-1 Schematic Diagram of Primary Packaging Containers . . . . .	1	206
Figure 3.3.2.2-2 Schematic Diagram of Secondary Packaging Commercial . . . . .	1	207
3.3.2.2.1 Qualification of Container and Closures . . . . .	1	208
Table 3.3.2.2-1 Low Density Polyethylene Resin Qualification Test Results . . . . .	1	208
Container Extractables . . . . .	1	208
3.3.2.2.3 Product Tests, Specifications, and Analytical Methods . . . . .	1	210
Table 3.3.2.3-1 Product Tests, Specifications, and Analytical Methods for Cyclosporin Ophthalmic Emulsion 0.1% . . . . .	1	210
Table 3.3.2.3-2 Product Tests, Specifications, and Analytical Methods for Cyclosporin Ophthalmic Emulsion 0.05% . . . . .	1	211
3.3.2.3.1 Rationale for Drug Product Specifications: . . . . .	1	211

Active Ingredient Concentration.....	1	211
Microscopic Appearance .....	1	211
Globule Size .....	1	211
Viscosity .....	1	212
Osmolality and pH .....	1	212
Physical Appearance.....	1	212
Sterility .....	1	212
Water Loss .....	1	212
3.3.2.3.2 Rationale for Analytical Tests for Drug Product:.....	1	212
Cyclosporine (Method AP-I.280-5) .....	1	213
Cyclosporine Identification (Appendix 4A5.5.3, Method AP-ID-088-1).....	1	214
Microscopic Appearance (Method AP-M003-1) .....	1	214
Globule Size: Single Particle Optical Sensing (Method AP-Z002-5) .....	1	214
Globule Size: Turbidity (Method AP-Z004-1).....	1	215
Viscosity (Method AP-V008-2) .....	1	215
Osmolality.....	1	215
Physical Appearance and pH (Method AP-MS005-2) .....	1	215
Sterility (SOP RSD.009).....	1	215
Stability Testing .....	1	216
3.3.2.3.3 Stability.....	1	216
3.3.6 CORRELATION OF DRUG SUBSTANCE LOTS USED IN CLINICAL, TOXICOLOGY, AND PRODUCT STABILITY LOTS ..	1	216
Table 3.3.6-1 Active Pharmaceutical Ingredient Lots Used in Clinical and Non-Clinical Studies .....	1	217
Table 3.3.6-2 Formulations Used in Non-Clinical Studies .....	1	222
3.4 NONCLINICAL SUMMARY .....	1	223
3.4.1 PHARMACOLOGY .....	1	223
3.4.2 TOXICOLOGY.....	1	224
3.4.3 PHARMACOKINETICS .....	1	225
3.5 CLINICAL PHARMACOKINETICS SUMMARY.....	1	226
3.5.1 SYSTEMIC EXPOSURE AFTER OPHTHALMIC ADMINISTRATION.....	1	226
Table 3.5.1-1. Comparison of dose and subsequent mean blood Cmax, Coverage, Cmin, and AUC0-12 between systemic therapeutic use of NEORAL® and topical use of 0.05% and 0.1% cyclosporine emulsions.....	1	227

3.5.2 OCULAR PHARMACOKINETICS AFTER OPHTHALMIC ADMINISTRATION . . . . .	1	227
3.6 MICROBIOLOGY SUMMARY . . . . .	1	228
3.7 CLINICAL SUMMARY . . . . .	1	229
3.7.1 CLINICAL PHARMACOLOGY AND PHARMACOKINETICS	1	229
3.7.1.1 Background . . . . .	1	229
3.7.1.2 Assessment of Immune Activation and Inflammatory Response . . . . .	1	229
3.7.1.3 Ocular Surface Inflammation . . . . .	1	230
3.7.1.4 Pharmacologic Activity . . . . .	1	231
Immunomodulation . . . . .	1	231
Anti-Inflammatory Activity . . . . .	1	232
Modulation of Pathological Apoptosis . . . . .	1	232
3.7.1.5 Conclusions . . . . .	1	233
3.7.1.6 References . . . . .	1	233
3.7.2 OVERVIEW OF CLINICAL STUDIES . . . . .	1	236
3.7.2.1 Introduction . . . . .	1	236
3.7.2.2 Design of the Phase 3 Clinical Trials . . . . .	1	236
Dosage . . . . .	1	236
Patient Selection Criteria . . . . .	1	237
Duration of Studies . . . . .	1	237
Timing of Visits . . . . .	1	237
Number of Patients . . . . .	1	237
Choice of Control . . . . .	1	238
Efficacy Endpoints in the Phase 3 Studies . . . . .	1	238
Pharmacokinetics . . . . .	1	240
Laboratory Testing . . . . .	1	240
Safety Testing . . . . .	1	240
3.7.2.3 FDA/Sponsor Discussions . . . . .	1	240
3.7.2.5 References . . . . .	1	242
Study Report References . . . . .	1	242
Literature References . . . . .	1	242
3.7.3 CONTROLLED CLINICAL STUDIES . . . . .	1	243
3.7.3.1 Introduction . . . . .	1	243
3.7.3.2 Tabular Presentation of Studies . . . . .	1	243
Table 3.7.3.2—1 Phase 2 Clinical Study 192371-001 . . . . .	1	244



Table 3.7.3.2—2 Phase 3 Clinical Study 192371-002 . . . . .	1	245
Table 3.7.3.2—3 Phase 3 Clinical Study 192371-003 . . . . .	1	246
3.7.3.3 Phase 2 Dose-Response Study. . . . .	1	247
Objective. . . . .	1	247
Design. . . . .	1	247
Study Population. . . . .	1	247
Evaluation Criteria . . . . .	1	247
Statistical Methods . . . . .	1	248
Patient Disposition and Demographics. . . . .	1	248
Table 3.7.3.3 Phase 2 Study: Summary of Demographics (ITT Population) . . . . .	1	249
Objective Efficacy Measures . . . . .	1	249
Subjective Efficacy Measures. . . . .	1	250
Other Measures . . . . .	1	251
Extent of Exposure . . . . .	1	251
Safety . . . . .	1	251
Conclusions. . . . .	1	252
3.7.3.4 Phase 3 Study Design . . . . .	1	252
Objective. . . . .	1	253
Design. . . . .	1	253
Study Population. . . . .	1	253
Evaluation Criteria . . . . .	1	253
Statistical Methods . . . . .	1	254
3.7.3.5 Phase 3 Patient Disposition and Demographics . . . . .	1	254
Table 3.7.3.5 Phase 3 Studies: Summary of Demographics (ITT Population). . . . .	1	255
3.7.3.6 Phase 3 Intent-to-Treat Analysis of Efficacy Results . . . . .	1	255
Objective Efficacy Measures . . . . .	1	256
Table 3.7.3.6—1 Corneal Fluorescein Staining in Phase 3 Studies (Intent-to-Treat Population) . . . . .	1	256
Table 3.7.3.6-2 Categorized Schirmer Values With Anesthesia in Phase 3 Studies (Intent-to-Treat Population) . . . . .	1	257
Subjective Efficacy Measures. . . . .	1	258
Table 3.7.3.6-3 Blurred Vision in Phase 3 Studies (Intent-to-Treat Population) . . . . .	1	259
Table 3.7.3.6—4 Daily REFRESH® Use During the Previous Week in Phase 3 Studies (Intent-to-Treat Population) . . . . .	1	260

Responder Analysis .....	1	261
Table 3.7.3.6—5 Number (%) of Responders in Phase 3 Studies (Intent-to-Treat Population) .....	1	261
Meta-Analysis .....	1	262
Table 3.7.3.6—6 Statistically Significant Among-Group Differences in the Meta-Analysis of Phase 3 Studies (Intent-to-Treat Population) .....	1	262
Subgroup Analyses .....	1	263
3.7.3.7 Results of Phase 3 Tertiary Ophthalmic Tests .....	1	263
Inflammatory Cytokine IL—6 Levels .....	1	263
Table 3.7.3.7—1 Normalized IL-6: Baseline Data and Change from Baseline at Months 3 and 6 .....	1	264
Lymphocytic and Immune Activation Markers from Conjunctival Biopsies .....	1	264
Table 3.7.3.7—2 Lymphocytic and Immune-Activation Markers: Baseline Data and Percent Change at Month 6 .....	1	265
Goblet Cell Density from Conjunctival Biopsies .....	1	266
Table 3.7.3.7—3 PAS/Goblet Cell Density from Conjunctival Biopsy: Baseline Data and Percent Change at Month 6 .....	1	266
3.7.3.8 Phase 3 Pharmacokinetics Results .....	1	267
3.7.3.9 Phase 3 Safety Results .....	1	267
Extent of Exposure .....	1	267
Adverse Events .....	1	267
Table 3.7.3.9—1 Number (%) of Patients in the Phase 3 Studies with Adverse Events Overall and by Body System (Intent-to-Treat Population) .....	1	268
Table 3.7.3.9—2 Number (%) of Patients in the Phase 3 Studies with Ocular Adverse Events Reported by 3% of Patients in a Treatment Group (Intent-to-Treat Population). 1		269
Other Safety Parameters .....	1	270
3.7.3.10 Dose and Regimen Rationale .....	1	270
3.7.3.11 Discussion .....	1	271
Efficacy .....	1	271
Safety .....	1	274
3.7.3.12 Conclusions .....	1	275
3.7.3.13 References .....	1	277
Study Report References .....	1	277
Literature References .....	1	279
3.7.4 OTHER STUDIES AND INFORMATION .....	1	281

3.7.5 SAFETY SUMMARY GENERAL SAFETY CONCLUSIONS . . . . .	1	282
3.7.5.1 Extent of Exposure . . . . .	1	282
3.7.5.2 Demographics and Other Patient Characteristics . . . . .	1	284
3.7.5.3 Adverse Events . . . . .	1	284
Adverse Events Regardless of Causality . . . . .	1	284
Table 3.7.5.3—1 Number (%) of Patients in the Phase 3 Studies with Adverse Events by Relationship to Study Medication and Severity . . . . .	1	285
Table 3.7.5.3—2 Number (%) of Patients in the Phase 3 Studies with Adverse Events Reported by 3% of Patients in Either Cyclosporine Group, Regardless of Causality . . . . .	1	286
Table 3.7.5.3—3 Number (%) of Patients in Phase 2 Study with Adverse Events, Regardless of Causality . . . . .	1	288
Serious Adverse Events . . . . .	1	288
Discontinuations Due to Adverse Events . . . . .	1	289
Adverse Events by Subgroup . . . . .	1	289
3.7.5.4 Laboratory Data. . . . .	1	290
Blood Chemistry and Hematology . . . . .	1	290
Ocular Microbiology. . . . .	1	290
Table 3.7.5.4 Number (%) of Patients in Phase 2 Study with Organisms Isolated . . . . .	1	291
3.7.5.5 Other Safety Assessments . . . . .	1	291
Visual Acuity . . . . .	1	291
Intraocular Pressure . . . . .	1	292
Biomicroscopy . . . . .	1	292
3.7.5.6 Drug-Drug Interactions . . . . .	1	292
3.7.5.7 Drug Abuse and Overdosage. . . . .	1	293
3.7.5.8 Safety Information from Other Sources. . . . .	1	293
Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Keratoconjunctivitis Sicca. . . . .	1	293
Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Other Indications. . . . .	1	293
In-House Animal Studies . . . . .	1	294
3.7.5.9 Discussion . . . . .	1	294
Ocular Safety . . . . .	1	294
Systemic Safety. . . . .	1	295
3.7.5.10 Conclusions . . . . .	1	297

3.7.5.11 References . . . . .	1	298
Study Report References. . . . .	1	298
Literature References . . . . .	1	300
<b>3.8 DISCUSSION OF THE BENEFIT/RISK RELATIONSHIP AND PROPOSED ADDITIONAL STUDIES . . . . .</b>	<b>1</b>	<b>304</b>
<b>3.8.1 BENEFIT/RISK ASSESSMENT OF CYCLOSPORINE     OPHTHALMIC EMULSION IN THE TREATMENT OF DRY EYE . . . . .</b>	<b>1</b>	<b>304</b>
3.8.1.1 Benefits . . . . .	1	304
3.8.1.2 Risks . . . . .	1	306
3.8.1.3 Conclusions . . . . .	1	308
<b>3.8.2 PROPOSED POST-MARKETING CLINICAL STUDIES OR     SURVEILLANCE . . . . .</b>	<b>1</b>	<b>309</b>
<b>3.8.3 REFERENCES . . . . .</b>	<b>1</b>	<b>310</b>
3.8.3.1 Study Report References . . . . .	1	310
3.8.3.2 Literature References. . . . .	1	312
<b>Section 4 CHEMISTRY MANUFACTURING and CONTROLS DATA . 2</b>	<b>2</b>	<b>004</b>
<b>4A CHEMISTRY, MANUFACTURING, AND CONTROLS . . . . .</b>	<b>2</b>	<b>004</b>
4A.2.4.2 Sampling Plan of Active Pharmaceutical Ingredient. . . . .	2	008
Requirements for Raw Material Sampling . . . . .	2	008
4A.3.4.3 Commercial Manufacturing Process . . . . .	2	009
Table 4A.3.4.3-1 In-Process Parts and Quantities Used to Manufacture a Commercial-scale Batch of Cyclosporine Ophthalmic Emulsion 0.05% (formula 9054X) . . . . .	2	009
Table 4A.3.4.3-2 In-Process Parts and Quantities Used to Manufacture a Commercial-scale Batch of Cyclosporine Ophthalmic Emulsion 0.1% (formula 8735X) . . . . .	2	010
4A.3.4.7 Commercial Scale Batch Results. . . . .	2	011
Table 4A.3.4.7 Testing Results for a Commercial-scale lot of Cyclosporine 0.1% w/w Emulsion (Bulk Lot No. 02104) . . . . .	2	012
Table 4A.3.4.7 Testing Results for a Commercial-scale lot of Cyclosporine 0.1% w/w Emulsion (Bulk Lot No. 02104) - continued. . . . .	2	013
4A.3.5 Container Closure System . . . . .	2	014
4A.3.5.1 Container and Closure Components. . . . .	2	014
Primary Packaging . . . . .	2	014
4A.3.5.3 Container and Closure Fabrication Materials . . . . .	2	015
Table 4A.3.5.3-1 Primary Container and Closure Fabrication Materials . . . . .	2	015
4A.3.6.3 Product Tests and Specifications. . . . .	2	016

Table 4A.3.6.3-1 Product Tests and Specifications for Cyclosporin A Ophthalmic Emulsion 0.1% . . . . .	2	016
Table 4A.3.6.3-2 Product Tests and Specifications for Cyclosporin A Ophthalmic Emulsion 0.05% . . . . .	2	017
4A.3.6.5 Drug Product Sampling Plans . . . . .	2	018
Procedure for Bulk Sampling . . . . .	2	018
Procedure for Sampling Final Product . . . . .	2	018
Procedure for Unit Dose Sampling . . . . .	2	018
4A.4 CORRELATION OF API LOTS AND FORMULATIONS USED IN CLINICAL AND NON-CLINICAL STUDIES . . . . .	2	019
Table 4A.4-1 Active Pharmaceutical Ingredient Lots Used in Clinical and Non-Clinical Studies . . . . .	2	019
Certificates of Analysis for Finished Product Lots . . . . .	2	026
LOT 10619 . . . . .	2	026
LOT 10621 . . . . .	2	029
LOT 10622 . . . . .	2	031
LOT 10650 . . . . .	2	033
LOT 10651 . . . . .	2	034
LOT 10718 . . . . .	2	035
LOT 10813 . . . . .	2	036
LOT 10814 . . . . .	2	037
LOT 11101 . . . . .	2	038
LOT 11102 . . . . .	2	041
LOT 11108 . . . . .	2	044
LOT 11110 . . . . .	2	047
LOT 11138 . . . . .	2	048
LOT 11139 . . . . .	2	051
LOT 11140 . . . . .	2	054
LOT 11141 . . . . .	2	055
LOT 11142 . . . . .	2	056
LOT 11143 . . . . .	2	057
LOT 11234 . . . . .	2	060
LOT 11235 . . . . .	2	061
LOT 11260 . . . . .	2	062
APPENDIX 4A.5.3.1 ONGOING STABILITY PROTOCOL . . . . .	2	063
APPENDIX 4A.5.3.2 ASEPTIC PROCESS VALIDATION REPORT . . . . .	2	065
PART IV ASEPTIC PROCESS VALIDATION . . . . .	2	065

A. BUILDING AND FACILITIES.....	2	065
1. DESIGN AND CONSTRUCTION FEATURES.....	2	065
a. Manufacturing Area - Room Construction and Maintenance	2	065
b. Form/Fill/Seal (Unit Dose) Filling Suites - Room Construction and Maintenance .....	2	066
2. LOCATION OF EQUIPMENT .....	2	067
a. Production - Ophthalmic Products .....	2	067
B. OVERALL MANUFACTURING PROCESS .....	2	067
EQUIPMENT STERILIZATION.....	2	068
MANUFACTURING PROCESS.....	2	069
Preparation of Part 1.....	2	069
Preparation of Part 2.....	2	070
Preparation of Part 3.....	2	070
Preparation of Part 4.....	2	071
PROCESSING SEQUENCE .....	2	071
Filter Integrity Testing.....	2	071
Product Transfer.....	2	071
Product Filling.....	2	072
NORMAL FLOW OF PRODUCT AND MATERIALS IN MANUFACTURING .....	2	072
Container/Closure Flow Diagram .....	2	073
Personnel Flow Diagram .....	2	073
Component Flow Diagram.....	2	073
Material Flow/Compounding Diagram .....	2	073
PROCESSING SEQUENCE .....	2	075
TRANSFER TO HOLDING VESSEL AND IN-PROCESS SAMPLING.....	2	075
STERILE BULK PRODUCT FLOW DIAGRAM.....	2	075
DRUG PRODUCT ASEPTIC MANUFACTURE.....	2	075
FILTERS .....	2	076
Part 1 Filtration .....	2	076
Part 2 Filtration .....	2	076
Part 4 Filtration .....	2	076
CONCERNING HOLDING PERIODS .....	2	077
CRITICAL OPERATIONS.....	2	077
C. STERILIZATION OF CONTAINERS, CLOSURES, EQUIPMENT, AND COMPONENTS .....	2	077

D. PROCEDURES AND SPECIFICATIONS FOR MEDIA FILLS .	2	078
DESCRIPTION OF THE ASEPTIC MANUFACTURING PROCESS VALIDATION . . . . .	2	078
Part 1 Oil Phase Manufacturing Process. . . . .	2	078
Part 2 Aqueous Phase (Water, Glycerin, Polysorbate 80) . . . .	2	079
Part 3 (Water, Pemulen). . . . .	2	079
Part 4 (1N Sodium Hydroxide) . . . . .	2	080
Fryma Processing Vessel. . . . .	2	080
MEDIA HOLD TESTS. . . . .	2	080
1. Type of medium used. . . . .	2	080
2. Incubation parameters . . . . .	2	080
3. Date of each media hold. . . . .	2	081
ASEPTIC FILLING UD#2. . . . .	2	081
1. The filling room . . . . .	2	081
2. The container-closure type and size. . . . .	2	081
3. The volume of medium used in each container . . . . .	2	082
4. Type of medium used. . . . .	2	082
5. Number of units filled . . . . .	2	082
6. Number of units incubated. . . . .	2	082
7. Number of positives. . . . .	2	082
8. Incubator parameters . . . . .	2	083
9. Date of each media fill. . . . .	2	083
10. Simulations. . . . .	2	083
11. Microbiological Monitoring. . . . .	2	083
12. Process Parameters. . . . .	2	083
E. ACTIONS CONCERNING PRODUCT WHEN MEDIA FILL FAILS. . . . .	2	084
F. MICROBIOLOGICAL MONITORING OF THE ENVIRONMENT. . . . .	2	084
1. MICROBIOLOGICAL METHODS. . . . .	2	084
a. Airborne microorganisms. . . . .	2	084
b. Microorganisms on inanimate surfaces . . . . .	2	085
c. Microorganisms on personnel . . . . .	2	085
d. Water systems . . . . .	2	085
e. Product component bioburden . . . . .	2	085
2. YEASTS, MOLDS, AND ANAEROBIC MICROORGANISMS. . . . .	2	085

3. EXCEEDED LIMITS . . . . .	2	086
G. CONTAINER CLOSURE AND PACKAGE INTEGRITY . . . . .	2	086
H. STERILITY TEST METHODS AND RELEASE CRITERIA . . . . .	2	086
I. BACTERIAL ENDOTOXINS TEST AND METHODS . . . . .	2	086
J. EVIDENCE OF FORMAL WRITTEN PROCEDURES . . . . .	2	086
PART V. MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: . . . . .	2	087
STABILITY CONSIDERATIONS. . . . .	2	087
A. CONTAINER-CLOSURE INTEGRITY . . . . .	2	087
B. PRESERVATIVE EFFECTIVENESS . . . . .	2	087
ATTACHMENTS . . . . .	2	088
SPQU-174 System Performance Qualification of Class 100 Point of Fill Equipment, ALP Filling Machine UD#2 . . . . .	2	089
SPQU-174 Protocol. . . . .	2	095
SPQU-174 Test Data. . . . .	2	102
SPQU-174 Microbiology Results . . . . .	2	190
EIQU-148 Computer System Validation - Fryma Processing Equipment . . . . .	2	220
EIQU-148 Addendum 1 . . . . .	2	235
EIQU-148 Addendum 2 . . . . .	2	289
EIQU-148 Tag Error. . . . .	2	294
EIQU-148 Recipe Function. . . . .	2	299
EIQU-148 E-Stop Action . . . . .	2	302
EIQU-148 Fault 274 . . . . .	2	304
EIQU-148 Addendum 3 . . . . .	2	325
EIQU-148 Protocol and Test Data . . . . .	2	362
EIQU-148 Addendum 4 . . . . .	3	108
EIQU-148 System Configuration Survey. . . . .	3	170
EIQU-148 Interface PC Directory Listings. . . . .	3	192
SPQU-194 SIP Performance Qualification for Fryma Equipment 4		001
SPQU-194 Certification . . . . .	4	024
SPQU-194 Certification Addendum 1 . . . . .	4	041
SPQU-194 Certification Addendum 2 . . . . .	4	047
SPQU-194 Certification Addendum 3 . . . . .	4	050
SPQU-194 SIP Performance Qualification. . . . .	4	065
SPQU-194 Thermocouple Pre-Calibration. . . . .	4	093



SPQU-194 Bulk Sterilization TC and BI Location. . . . .	4	120
SPQU-194 Bulk Sterilization Study C.01. . . . .	4	126
SPQU-194 Bulk Sterilization Study, C.02 . . . . .	4	172
SPQU-194 Bulk Sterilization Study C.01, cont. . . . .	4	224
SPQU-194 Bulk Sterilization Study D.01. . . . .	4	253
SPQU-194 Bulk Sterilization Study D.01, cont. . . . .	4	301
SPQU-194 Bulk Sterilization Study D.02. . . . .	5	001
SPQU-194 Bulk Sterilization Study D.03. . . . .	5	060
SPQU-194 Bulk Sterilization Study D.04. . . . .	5	122
SPQU-194 Thermocouple Post-Calibration . . . . .	5	181
SPQU-194 Performance Qualification Summary. . . . .	5	196
SPQU-194 SIP Performance Qualification for Fryma Equipment, Addendum 2 . . . . .	5	198
SPQU-194 Addendum 2 Protocol. . . . .	5	204
SPQU-194 Addendum 2 Procedure 1. . . . .	5	210
SPQU-194 Addendum 2 Procedure 2, Run 1 . . . . .	5	228
SPQU-194 Addendum 2 Procedure 2, Run 2 . . . . .	5	290
SPQU-194 Addendum 2 Procedure 2, Run 3 . . . . .	5	346
SPQU-194 Addendum 3 Protocol. . . . .	6	001
SPQU-194 Addendum 3 Thermocouple Pre-Calibration . . . . .	6	020
SPQU-194 Addendum 3 TCBI Location . . . . .	6	049
SPQU-194 Addendum 3 TCBI Study F.01. . . . .	6	057
SPQU-194 Addendum 3 TCBI Study F.02. . . . .	6	096
SPQU-194 Addendum 3 TCBI Study F.02, cont. . . . .	6	148
SPQU-194 Addendum 3 TCBI Study F.03. . . . .	6	198
SPQU-194 Addendum 3 TCBI Study F.03, cont. . . . .	6	253
SPQU-194 Addendum 3 TCBI Study F.04. . . . .	6	309
SPQU-194 Addendum 3 TCBI Study F.04, cont. . . . .	6	359
SPQU-194 Addendum 3 Thermocouple Post-Calibration . . . . .	7	001
SPQU-194 Addendum 3 Summary. . . . .	7	010
SPQU-194 Addendum 4. . . . .	7	013
SPQU-194 Addendum 4 Protocol. . . . .	7	018
SPQU-194 Addendum 4 Procedure 1. . . . .	7	025
SPQU-194 Addendum 4 Procedure 2. . . . .	7	043
SPQU-194 Addendum 4 Procedure 3. . . . .	7	053

SPQU-209 Steaming of CST-1, CST-2 and Material Transfer System .....	7	101
SPQU-209 Protocol .....	7	110
SPQU-209 Procedure 1 .....	7	118
SPQU-209 Procedure 2 .....	7	134
SPQU-209 BI Test Data .....	7	185
SPQU-203 Annual SIP Cycle Verification of UD#2 .....	7	205
SPQG-140 Annual Revalidation of the Compounding Finn Aqua Autoclave .....	8	001
SPQG-140 Protocol - Autoclave .....	8	008
SPQG-140 Procedure 1 .....	8	023
SPQG-140 Procedure 2 .....	8	076
SPQG-140 Procedure 3 .....	8	082
SPQG-140 Procedure 4 .....	8	134
SPQG-140 Procedure 5 .....	8	196
SPQG-140 Procedure 6 .....	8	255
SPQG-140 Procedure 7 .....	8	298
SPQG-140 BI Test Data .....	8	340
PRODUCT FLOW DIAGRAMS .....	8	359
CONTAINER/CLOSURE FLOW DIAGRAM 1 .....	8	360
PERSONNEL FLOW DIAGRAM 2 .....	8	361
COMPONENT FLOW DIAGRAM 3 .....	8	362
MATERIAL FLOW/COMPOUNDING DIAGRAM 4 .....	8	363
STERILE BULK PRODUCT FLOW DIAGRAM 5 .....	8	364
SVU-139 Aseptic Manufacturing of Cyclosporine Sterile Ophthalmic Emulsion .....	9	001
SVU-139 Protocol .....	9	010
Report VR-R20-P-141 Validation Report Cyclosporine Oil Phase (Part I) Filtration .....	9	034
Report VR-R20-P-141 Validation Protocol .....	9	044
Report VR-R20-P-141 Product Flush Volume Results .....	9	048
Report VR-R20-P-141 Pall Report 6059 .....	9	049
Report VR-R20-P-141 Pall Report 6234 .....	9	073
Report VR-R20-P-141 Chemical Compatibility Results .....	9	094
Report VR-R20-P-141 Pall Report 6130 .....	9	095
Report VR-R20-P-141 Filter Integrity .....	9	104
Report VR-R20-P-141 Allergan Reports .....	9	111

Report VR-N38-P-136 Validation Report Gelman Supor® DCF Capsule Filtration with Cyclosporine (Aqueous Phase) Solution .	9	116
Report VR-N38-P-136 Appendix A . . . . .	9	172
Report 7770 Validation of Pall SuporFlow® 200 Filter Medium for 0.1N Sodium Hydroxide . . . . .	9	215
SPQU-179 SIP Verification of UD2 . . . . .	9	239
Protocol SIP Verification. . . . .	9	246
Protocol Addendum 1 . . . . .	9	253
Data Sheet Procedure 1 . . . . .	9	256
SPQU-179 SIP Verification of UD2 part 2. . . . .	9	289
SPQU-179 SIP Verification of UD2 part 3. . . . .	9	336
WQM-057 Media Fill Procedure and Documentation. . . . .	10	001
WMD-035 Unit Dose Media Fill Operation . . . . .	10	004
SVU-133 UD2 Media Fill Procedure . . . . .	10	010
SVU-133 Protocol - Media Fill Procedure . . . . .	10	014
SVU-133 Protocol Addendum 1 . . . . .	10	020
SVU-133 Microbiology Summary . . . . .	10	023
SVU-133 Manufacturing Results . . . . .	10	055
SVU-133 Test Data. . . . .	10	057
SVU-141 UD2 Media Fill Procedure . . . . .	10	143
SVU-141 Protocol - Media Fill Procedure . . . . .	10	147
SVU-141 Microbiology Summary . . . . .	10	153
SVU-141 Manufacturing Results . . . . .	10	193
SVU-141 Test Data. . . . .	10	195
SVU-148 UD2 Media Fill Procedure . . . . .	10	267
SVU-148 Protocol. . . . .	10	271
SVU-148 Microbiology Summary . . . . .	10	277
SVU-148 Manufacturing Results . . . . .	10	312
SVU-148 Test Data. . . . .	10	314
WQM-012 Environmental Monitoring . . . . .	11	001
BTC Study 40402 Package Integrity . . . . .	11	040
SOP Index. . . . .	11	046
<b>APPENDIX 4A.5.7 REPRESENTATIVE MANUFACTURING AND QUALITY MASTER RECORDS. . . . .</b>	<b>11</b>	<b>089</b>
Manufacturing Record. . . . .	11	090
Manufacturing Procedure . . . . .	11	092

Product Specifications . . . . .	11	108
Analysis Procedure . . . . .	11	109
APPENDIX 4A.5.8 ENVIRONMENTAL ASSESSMENT REPORT . .	11	112
4B SAMPLES . . . . .	11	113
Table 4B.1 Tabular listing of all samples to be submitted . . . . .	11	113
4C METHODS VALIDATION . . . . .	12	001
4C. METHODS VALIDATION PACKAGE . . . . .	12	001
Table 4C.1 Cross-Reference to NDA Section 4A . . . . .	12	002
Table 4C.1 Cross-Reference to NDA Section 4A for detailed information . . . . .	12	003
4C.1 ACTIVE PHARMACEUTICAL INGREDIENT . . . . .	12	004
4C.1.1 ACTIVE PHARMACEUTICAL INGREDIENT DESCRIPTION . . . . .	12	005
4C.1.2 ACTIVE PHARMACEUTICAL INGREDIENT SPECIFICATIONS, ANALYTICAL METHODS AND RATIONALE . . . . .	12	008
4C.1.3 ACTIVE PHARMACEUTICAL INGREDIENT LOT ANALYSIS . . . . .	12	009
4C.1.4 ACTIVE PHARMACEUTICAL INGREDIENT CERTIFICATES OF ANALYSIS . . . . .	12	012
4C.2 REFERENCE STANDARD . . . . .	12	018
4C.3 DOSAGE FORM [DRUG PRODUCT] . . . . .	12	019
4C.3.1 LIST OF COMPONENTS . . . . .	12	019
4C.3.2 STATEMENT OF COMPOSITION . . . . .	12	020
4C.3.3 SPECIFICATIONS, ANALYTICAL METHODS AND RATIONALE . . . . .	12	024
4C.4 CORRELATION OF LOTS . . . . .	12	032
Table 4A.4-1 Active Pharmaceutical Ingredient Lots Used in Clinical and Non-Clinical Studies (Original) . . . . .	12	032
4C.4 CORRELATION OF LOTS AND CERTIFICATES OF ANALYSES . . . . .	12	038
Table 4A.4-1 Active Pharmaceutical Ingredient Lots Used in Clinical and Non-Clinical Studies (Revised) . . . . .	12	038
Certificates of Analysis for Finished Product Lots . . . . .	12	045
LOT 10619 . . . . .	12	045
LOT 10621 . . . . .	12	048
LOT 10622 . . . . .	12	050
LOT 10650 . . . . .	12	052
LOT 10651 . . . . .	12	053

LOT 10718 .....	12	054
LOT 10813 .....	12	055
LOT 10814 .....	12	056
LOT 11101 .....	12	057
LOT 11102 .....	12	060
LOT 11108 .....	12	063
LOT 11110 .....	12	066
LOT 11138 .....	12	067
LOT 11139 .....	12	070
LOT 11140 .....	12	073
LOT 11141 .....	12	074
LOT 11142 .....	12	075
LOT 11143 .....	12	076
LOT 11234 .....	12	079
LOT 11235 .....	12	080
LOT 11260 .....	12	081
<b>4C.5 APPENDICES .....</b>	<b>12</b>	<b>082</b>
4A.5.1.1 Authorization Letters .....	12	083
4A.5.5.2 Assay AP-L280-5 HPLC Analysis Procedure for Cyclosporin A and Related Substances .....	12	087
4A.5.5.3 Assay AP-ID088-1 Identification Procedure for AGN 192371 by Thin Layer Chromatography .....	12	128
4A.5.5.4 Assay AP-M003-1 Procedure for Determining the Microscopic Appearance (PMA) of AGN 192371 Ophthalmic Emulsion .....	12	137
4A.5.5.5 Assay AP-Z002-5 Procedure for Determining the Oil Globule Size Distribution (OGS) of Cyclosporine Ophthalmic Emulsion by Single Particle Optical Snesing .....	12	145
4A.5.5.6 Assay AP-Z004-1 Procedure for Determining the Turbidity (NTU) of Cyclosporine Ophthalmic Emulsion .....	12	159
4A.5.5.7 Assay AP-V-008-2 Analysis Procedure of Cyclosporine Ophthalmic Emulsion by Rotational Viscosity (VIS) .....	12	168
4A.5.5.8 Assay AP-MS005-2 Procedure for Performing Physical Appearance and pH Testing of Emulsions .....	12	177
<b>Section 5 NONCLINICAL DATA .....</b>	<b>13</b>	<b>011</b>
5.1 LIST OF ABBREVIATIONS .....	13	011
5.2 ALLERGAN CONTACT PERSON .....	13	014
5.3 OVERVIEW .....	13	015

5.3.1 PHARMACOLOGY .....	13	015
5.3.2 TOXICOLOGY .....	13	016
5.3.3 PHARMACOKINETICS .....	13	017
5.3.4 CONTAINER/CLOSURE EXTRACTABLE STUDIES .....	13	018
5.4 PHARMACOLOGY .....	13	019
5.4.1 BACKGROUND .....	13	019
5.4.2 OCULAR SURFACE PHYSIOLOGY .....	13	019
5.4.3 PATHOPHYSIOLOGY OF DRY EYE .....	13	020
5.4.3.1 Background Environment .....	13	020
5.4.3.2 Neurogenic Inflammation .....	13	021
5.4.3.3 Initiating the Local Autoimmune Response .....	13	021
5.4.3.4 Immune Secretory Dysfunction in Non- Sjögren's Patients ..	13	022
5.4.3.5 Ocular Surface Inflammation .....	13	023
5.4.3.6 Dry Eye Dog Model .....	13	024
Methods .....	13	024
Table 5.4.3.6-1 .....	13	026
Results .....	13	033
Table 5.4.3.6-2 The Level of Apoptosis in the Nictitans Lacrimal Gland of Normal and Dry Eye Dogs (Bio-98-275) ..	13	034
Conclusions .....	13	034
5.4.4 PRIMARY PHARMACOLOGY ACTIVITY / MECHANISM OF ACTION .....	13	034
5.4.4.1 Immunomodulation .....	13	035
5.4.4.2 Cellular Mechanism of Action .....	13	036
5.4.5 SECONDARY PHARMACOLOGY ACTIVITY .....	13	036
5.4.5.1 Anti-Inflammatory Activity .....	13	036
5.4.5.2 Modulation of Apoptosis .....	13	038
Conclusions .....	13	039
5.4.6 REFERENCES .....	13	040
5.4.6.1 Study Report References .....	13	040
5.4.6.2 Literature References .....	13	041
5.5 TOXICOLOGY .....	13	047
5.5.1 OVERVIEW .....	13	047
5.5.1.1 Ocular Safety .....	13	047
5.5.1.2 Systemic Safety .....	13	048

Table 5.5.1.2 Pharmacokinetic parameters of cyclosporin A in rabbit or dog blood after unilateral ophthalmic instillation of cyclosporine emulsion (mean $\pm$ standard deviation) . . . . .	13	049
5.5.1.3 Margin of Safety . . . . .	13	049
Margin of safety based on the ocular dose (mg/kg/day). . . . .	13	050
Margin of safety based on the drug levels (Cmax). . . . .	13	050
Table 5.5.1.3 Maximum blood concentrations in animals after oral administration of cyclosporine at the no effect level dose and margin of safety . . . . .	13	050
5.5.2 SINGLE DOSE TOXICITY . . . . .	13	050
5.5.3 REPEATED DOSE TOXICITY . . . . .	13	051
5.5.3.1 Individual Study Summaries . . . . .	13	051
A Three-Month Ocular and Systemic Toxicity Study with a One-Month Recovery Period in New Zealand White Rabbits. . . . .	13	051
A Six-Month Ocular and Systemic Toxicity Study with a Two-Month Recovery Period in New Zealand White Rabbits . . . . .	13	052
52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period . . . . .	13	053
5.5.3.2 Tabular Summary . . . . .	13	055
5.5.3.2-1 A Three-Month Ocular and Systemic Toxicity Study with a One-Month Recovery Period in New Zealand White Rabbits . . . . .	13	055
5.5.3.2-2 A Six-Month Ocular and Systemic Toxicity Study with a 2-Month Recovery Period in New Zealand White Rabbits . . . . .	13	056
5.5.3.2-3 52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period. . . . .	13	057
5.5.4 CARCINOGENICITY . . . . .	13	058
5.5.5 SPECIAL TOXICITY . . . . .	13	058
5.5.6 REPRODUCTION . . . . .	13	058
5.5.7 MUTAGENICITY. . . . .	13	058
5.5.8 REFERENCES . . . . .	13	058
5.5.8.1 Study Report References . . . . .	13	058
5.5.8.2 Literature References. . . . .	13	058
5.6 ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION . . . . .	13	061
5.6.1 OVERVIEW . . . . .	13	061
5.6.1.1 Ocular Pharmacokinetics after Ophthalmic Administration . . . . .	13	061
Formulation Selection and Characterization. . . . .	13	062
Ocular Metabolism . . . . .	13	062

Ocular Absorption, Distribution, and Elimination . . . . .	13	062
5.6.1.2 Systemic Exposure after Ophthalmic Administration . . . . .	13	064
Table 5.6.1.2-1. Comparison of dose and subsequent mean blood Cmax, Coverage, Cmin, and AUC0-12 between systemic therapeutic use of NEORAL® and topical use of 0.05% and 0.1% cyclosporine emulsions. . . . .	13	066
5.6.2 TABULAR SUMMARY . . . . .	13	067
5.6.2.1 Tabular Summary of Ocular Pharmacokinetics in Rabbits and Dogs . . . . .	13	067
Table 5.6.2.1-1 Comparison of ocular tissue concentrations of cyclosporine after topical instillation of 6 formulations of 3H-cyclosporine to rabbit eyes . . . . .	13	067
Table 5.6.2.1-2 Investigation of ocular metabolism of cyclosporine after a single eyedrop instillation of a 0.2% 3H-cyclosporine ophthalmic emulsion into albino rabbit eyes . . .	13	068
Table 5.6.2.1-3 Dose proportionality of ocular tissue 3H-cyclosporine concentrations after a single dose administration of 0.05%, 0.2%, and 0.4% 3H-cyclosporine emulsions into rabbit eyes . . . . .	13	069
Table 5.6.2.1-4 The effect of oil globule size on ocular absorption of 3H-cyclosporine after topical instillation of three 0.2% 3H-cyclosporine oil-in-water emulsions into albino rabbit eyes . .	13	070
Table 5.6.2.1-5 Ocular pharmacokinetics of cyclosporine after a single eyedrop instillation of a 0.2% 3H-cyclosporine ophthalmic emulsion into albino rabbit eyes . . . . .	13	071
Table 5.6.2.1-6 Ocular cyclosporine distribution during 9 1/2 days of dosing of 0.05 and 0.1% 3H-cyclosporine emulsions to albino rabbit eyes . . . . .	13	072
Table 5.6.2.1-7 3H-cyclosporine ocular absorption and disposition in beagle dogs following single ocular doses of 0.2% 3H-cyclosporine emulsion . . . . .	13	073
Table 5.6.2.1-8 3H-Cyclosporine ocular absorption and disposition in beagle dogs following multiple ocular doses of 0.2% 3H-cyclosporine emulsion . . . . .	13	074
5.6.2.2 Tabular Summary of Systemic Exposure after Topical Administration to Rabbits, Dogs, and Humans . . . . .	13	075
Table 5.6.2.2-1 Pharmacokinetic analysis of cyclosporine in rabbit blood for study No. 1793-2936-5 titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Three-Month Ocular and Systemic Toxicity Study with a One Month Recovery Period in New Zealand White Rabbits. . . . .	13	075



Table 5.6.2.2-2 Pharmacokinetic analysis of cyclosporin A in rabbit blood for study No. 1793-2936-6 titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Six-Month Ocular and Systemic Toxicity Study with a Two Month Recovery Period in New Zealand White Rabbits . . . . .	13	076
Table 5.6.2.2-3 Twelve-month toxicokinetic report: Pharmacokinetic analysis of cyclosporin A in dog blood for study No. HWA 985-126 titled "52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period" . . . . .	13	077
Table 5.6.2.2-4 Pharmacokinetic analysis of cyclosporin A in human blood for clinical study 192371-001 entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca. . . . .	13	078
Table 5.6.2.2-5 Six month interim pharmacokinetic analysis of cyclosporin A in human blood for clinical study 192371-002 entitled "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." . . . . .	13	079
Table 5.6.2.2-6 Interim report of blood cyclosporin A concentrations during one dosing interval for study 192371-002 titled, "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." . . . . .	13	080
5.6.3 INDIVIDUAL STUDY SUMMARIES . . . . .	13	081
5.6.3.1 Bioanalytical Methods. . . . .	13	081
Liquid Scintillation Analyses . . . . .	13	081
Liquid Chromatographic/Mass Spectroscopy-Mass Spectroscopy Methods . . . . .	13	081
5.6.3.2 Ocular Pharmacokinetic Studies in Animals and Humans . . .	13	082
Comparison of Ocular Tissue Concentrations of Cyclosporin-A after Topical Instillation of Six Formulations of 3H-Cyclosporin-A into Rabbit Eyes (Allergan Report PK-94-012) . . . . .	13	082
Table 5.6.3.2-1 Rank order of cyclosporine formulations in terms of radioactivity C <sub>max</sub> in ocular tissues (N=6) after instillation of a single eyedrop. A ranking of "1" indicates relatively high concentrations; "4" indicates low concentrations. . . . .	13	083

Investigation of Ocular Metabolism of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes (Allergan Report PK-95-011) . . . . .	13	084
Dose Proportionality of Ocular Tissue 3H-Cyclosporine Concentrations after a Single Dose Administration of 0.05%, 0.2%, and 0.4% 3H-Cyclosporine Emulsions into Rabbit Eyes (Allergan Report PK-96-011) . . . . .	13	084
Table 5.6.3.2-2 Pharmacokinetic parameters of cyclosporine in albino rabbit ocular tissues after a single dose of ophthalmic 0.05, 0.2, or 0.4% cyclosporine emulsions. . . . .	13	085
The Effect of Oil Globule Size on Ocular Absorption of 3H-Cyclosporine after Topical Instillation of Three 0.2% 3H-Cyclosporine Oil-in-Water Emulsions into Albino Rabbit Eyes (Allergan Report PK-95-074) . . . . .	13	086
Table 5.6.3.2-3 Pharmacokinetic parameters of cyclosporine in rabbit ocular tissues after a single ophthalmic dose of 0.2% cyclosporine emulsions containing small (< 10 μm), intermediate (~50-100 μm), or large (> 200 μm) oil globules. . . . .	13	087
Ocular Pharmacokinetics of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes (Allergan Report PK-95-010) . . . . .	13	087
Ocular Cyclosporine Distribution During 9 1/2 Days of Dosing of 0.05 and 0.1% 3H-Cyclosporine Emulsions to Albino Rabbit Eyes (Allergan Report PK-98-074) . . . . .	13	089
Table 5.6.3.2-4 Pharmacokinetic parameters of radioactivity in selected ocular tissues after 9 1/2 days of ophthalmic BID instillation of 0.05 or 0.1% cyclosporine emulsion to albino rabbits. . . . .	13	089
3H-Cyclosporine Ocular Absorption and Disposition in Beagle Dogs Following Single Ocular Doses of 0.2% 3H-Cyclosporine Emulsion (Allergan Report PK-96-017) . . . . .	13	090
3H-Cyclosporine Ocular Absorption and Disposition in Beagle Dogs Following Multiple Ocular Doses of 0.2% 3H-Cyclosporine Emulsion (Allergan Report PK-96-016) . . . . .	13	091
5.6.3.3 Systemic Pharmacokinetic Studies in Animals and Humans .	13	092
The Blood-to-Plasma Concentration Ratio of 3H-Cyclosporin-A in Mouse, Rat, Rabbit, Dog, and Human In Vitro (Allergan Report PK-94-108). . . . .	13	092
Table 5.6.3.3-1 In vitro blood/plasma ratios (mean ± SD, N=3) of cyclosporine concentrations in mouse, rat, rabbit, dog, and humans at 37°C. . . . .	13	093

Pharmacokinetic Analysis of Cyclosporine in Rabbit Blood for Study No. 1793-2936-5 Titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Three-Month Ocular and Systemic Toxicity Study with a One Month Recovery Period in New Zealand White Rabbits (Allergan Report PK-95-012) . . . . .	13	093
Table 5.6.3.3-2 Pharmacokinetic parameters of cyclosporin A in rabbit blood after 3 months of ophthalmic instillation of 0.05, 0.2, or 0.4% cyclosporine emulsions to 1 eye TID at 3 hour intervals. . . . .	13	094
Pharmacokinetic Analysis of Cyclosporin A in Rabbit Blood for Study No. 1793-2936-6 Titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Six-Month Ocular and Systemic Toxicity Study with a Two Month Recovery Period in New Zealand White Rabbits (Allergan Report PK-95-066) . . . . .	13	095
Table 5.6.3.3-3 Pharmacokinetic parameters of cyclosporin A in rabbit blood after 6 months of unilateral ophthalmic instillation of 0.05, 0.2, or 0.4% cyclosporine emulsions TID at 3 hour intervals or 0.4% cyclosporine emulsion 6 times daily at 2 hour intervals (6x/day). . . . .	13	095
Twelve-Month Toxicokinetic Report: Pharmacokinetic Analysis of Cyclosporin A in Dog Blood for Study No. HWA 985-126 Titled "52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period" (Allergan Report PK-96-023) . . . . .	13	096
Table 5.6.3.3-4 Pharmacokinetic parameters of cyclosporin A in dog blood after 1 and 49 weeks of unilateral ophthalmic instillation of 0.1 and 0.2% cyclosporine emulsions given 3 times daily at ~3 hour intervals, or 0.4% cyclosporine emulsion given 6 times daily at ~2 hour intervals. . . . .	13	096
Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca" (Allergan Report PK-96-018) . . . . .	13	097
Table 5.6.3.3-5 Trough and maximum concentrations of cyclosporin A in human blood after ophthalmic administration of 0.05, 0.1, 0.2 or 0.4% cyclosporine emulsion twice-daily to each eye for 12 weeks. . . . .	13	097
Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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." (Allergan Report PK-98-109). . . . .	13	098

Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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." (Allergan Report PK-98-112). . . . .	13	099
5.6.4 INTEGRATED TABULAR SUMMARY . . . . .	13	100
Table 5.6.4-1 Ocular cyclosporine concentrations after topical instillation of 0.05-0.4% 3H-cyclosporine emulsions to rabbits and dogs. . . . .	13	100
Table 5.6.4-2 Blood cyclosporine concentrations after topical instillation of 0.05-0.4% 3H-cyclosporine emulsions to rabbits, dogs, and humans. . . . .	13	107
5.6.5 ADME REFERENCES . . . . .	13	115
5.6.5.1 ADME Study Report References. . . . .	13	115
5.6.5.2 ADME Literature References . . . . .	13	118
5.7 LIST OF NON-CLINICAL PROFESSIONALS . . . . .	13	119
5.7.1 NON-CLINICAL GLP STUDY SITES AND STUDY DIRECTORS . . . . .	13	119
5.7.2 NON-CLINICAL EVALUATORS. . . . .	13	119
5.7.2.1 Curriculum Vitae . . . . .	13	121
Acheampong . . . . .	13	121
Angelov. . . . .	13	131
Brar . . . . .	13	138
Palmer. . . . .	13	149
Salome. . . . .	13	155
Small . . . . .	13	158
Tang-Liu . . . . .	13	164
Yuan . . . . .	13	190
Wadkins . . . . .	13	194
Wiese. . . . .	13	196
5.7.3 CONSULTANT PATHOLOGIST/TOXICOLOGIST . . . . .	13	202
5.7.3.1 Curriculum Vitae . . . . .	13	203
Dalgard . . . . .	13	203
Dyke . . . . .	13	211
Rubin. . . . .	13	216
Ridder . . . . .	13	233
Pearson . . . . .	13	238

Cardy.....	13	247
Thakur.....	13	256
5.8 DESCRIPTION OF CONTRACT LABORATORIES.....	13	266
Covance Facilities.....	13	267
5.9 SUMMARY OF FORMULATIONS USED IN NON-CLINICAL STUDIES.....	13	274
Table 5.9 Formulations Used in Non-Clinical Studies.....	13	274
5.10 GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT.....	13	275
5.11 NONCLINICAL STUDY REPORTS.....	13	276
DM-1/8/30/88 Cyclosporine-3H: Ocular absorption and penetration following topical applicaiton of a 2% ointment prepared with a solution of cyclosporine in corn oil.....	13	276
DM-1-7/15/91 3H Cyclosporin: Ocular absorption and penetration in the rabbit following single and multiple topical applicaiton of a 0.2% ointment prepared with a solution of cyclosporine in corn oil.....	13	296
BIO-98-274 Topical ophthalmic evaluation of cyclosporine (0.05%,0.2% bid for 12 weeks) in dry eye dogs.....	13	342
BIO-98-275 Evaluation of topical cyclosporine (0.2% bid for 12 weeks) in dry eye dogs. Effects on lymphocytic and acinar epithelial cell apoptosis are evaluated.....	13	356
1793-2936-5 AGN 192371 - Cyclosporine ophthalmic emulsion: A Three-month Ocular and Systemic Toxicity Study with a One-month Recovery Period in New Zealand White Rabbits.....	14	001
1793-2936-5 Appendix I Study Protocol and Amendments.....	14	085
1793-2936-5 Appendix II Test Article Data.....	14	108
1793-2936-5 Appendix III Toxicokinetic Group Data.....	14	127
1793-2936-5 Appendix IV Weekly Gross Ocular Observations.....	14	129
1793-2936-5 Appendix V Individual Ophthalmoscopic Data.....	14	152
1793-2936-5 Appendix VI Individual Slit Lamp Data.....	14	167
1793-2936-5 Appendix VII Individual Body Weights.....	14	182
1793-2936-5 Appendix VIII Individual Hematology Data.....	14	191
1793-2936-5 Appendix IX Individual Blood Chemistry Data.....	14	226
1793-2936-5 Appendix X Pharmacokinetics Report.....	14	261
1793-2936-5 Appendix XI Individual Gross Necropsy Data.....	14	279
1793-2936-5 Appendix XII Individual Organ Weights.....	14	282
1793-2936-5 Appendix XIII Individual Histological Findings.....	14	291
1793-2936-6 AGN 192371 - Cyclosporine ophthalmic emulsion: A Six-month Ocular and Systemic Toxicity Study with a Two-month Recovery Period in New Zealand White Rabbits.....	15	001

1793-2936-6 Appendix I Study Protocol and Amendments . . . . .	15	124
1793-2936-6 Appendix II Test Article Data . . . . .	15	148
1793-2936-6 Appendix III Toxicokinetic Group Data . . . . .	15	171
1793-2936-6 Appendix IV Weekly Gross Ocular Observations. . . . .	15	176
1793-2936-6 Appendix V Individual Ophthalmoscopic Data. . . . .	15	221
1793-2936-6 Appendix VI Individual Slit Lamp Data . . . . .	15	251
1793-2936-6 Appendix VII Individual Body Weights . . . . .	15	284
1793-2936-6 Appendix VIII Individual Hematology Data. . . . .	15	301
1793-2936-6 Appendix IX Individual Blood Chemistry Data . . . . .	16	001
1793-2936-6 Appendix X Pharmacokinetics Report. . . . .	16	087
1793-2936-6 Appendix XI Individual Gross Necropsy Data. . . . .	16	108
1793-2936-6 Appendix XII Individual Organ Weights . . . . .	16	114
1793-2936-6 Appendix XIII Individual Histological Data . . . . .	16	127
CHV-985-126 52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period . . . . .	17	001
CHV-985-126 Tables 1A-1E Summary Incidence of Clinical Observations. . . . .	17	050
CHV-985-126 Table 2 Mean Body Weights . . . . .	17	066
CHV-985-126 Table 3 Mean Food Consumption . . . . .	17	071
CHV-985-126 Table 4 Blood Pressure Data . . . . .	17	076
CHV-985-126 Table 5 Clinical Hematology Data. . . . .	17	079
CHV-985-126 Table 6 Clinical Chemistry Data . . . . .	17	103
CHV-985-126 Table 7A-7B Gross Pathology . . . . .	17	117
CHV-985-126 Table 8A Organ Weight Data. . . . .	17	121
CHV-985-126 Table 8B Organ Weight Data. . . . .	17	148
CHV-985-126 Table 9A-9B Histopathology . . . . .	17	162
CHV-985-126 Appendix 1A Individual Clinical Observations - Weekly . . . . .	17	178
CHV-985-126 Appendix 1B Individual Clinical Observations - Predose Ocular . . . . .	17	214
CHV-985-126 Appendix 1C Individual Clinical Observations - Postdose Ocular . . . . .	17	228
CHV-985-126 Appendix 1D Individual Clinical Observations - Ophthalmoscopic . . . . .	17	246
CHV-985-126 Appendix 1E Individual Clinical Observations - Slit Lamp. . . . .	17	259
CHV-985-126 Appendix 2 Body Weight. . . . .	17	268
CHV-985-126 Appendix 3 Food Consumption . . . . .	17	275

CHV-985-126 Appendix 5A Clinical Hematology . . . . .	17	285
CHV-985-126 Appendix 5B Clinical Hematology Unscheduled. . . . .	17	323
CHV-985-126 Appendix 6A Clinical Chemistry . . . . .	17	333
CHV-985-126 Appendix 6B Clinical Chemistry Unscheduled . . . . .	17	347
CHV-985-126 Appendix 7 Urinalysis . . . . .	17	351
CHV-985-126 Appendix 8 Animal Summary Data . . . . .	18	001
CHV-985-126 Appendix 9 Study Protocol. . . . .	18	101
CHV-985-126 Appendix 10 Protocol Deviations. . . . .	18	121
CHV-985-126 Attachment 1 Pharmacokinetics Report . . . . .	18	124
CHV-985-126 Attachment 2 Certificate of Analysis . . . . .	18	153
PK-94-012 Comparison of Ocular Tissue Concentrations of Cyclosporin-A after Topical Instillation of Six Formulations of 3H-Cyclosporin-A into Rabbit Eyes . . . . .	18	169
PK-94-108 The Blood-to-Plasma Concentration Ratio of 3H-Cyclosporin-A in Mouse, Rat, Rabbit, Dog, and Human In Vitro . . . . .	18	187
PK-95-008 Validation of the Analysis of Cyclosporin A Concentrations in Rabbit Blood by Liquid Chromatography/Mass Spectrometry/Mass Spectrometry . . . . .	18	197
PK-95-009 Quantitation of Cyclosporin A Concentrations in Rabbit Blood by Liquid Chromatography/Mass Spectrometry/Mass Spectrometry for Study 1793-2936-5, "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Three Month Ocular and Systemic Toxicity Study with a One Month Recovery Period in New Zealand White Rabbits" . . . . .	18	222
PK-95-010 Ocular Pharmacokinetics of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes . . . . .	18	257
PK-95-011 Investigation of Ocular Metabolism of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes . . . . .	18	289
PK-95-012 Pharmacokinetics Analysis of Cyclosporine in Rabbit Blood for Study No. 1793-2936-5 Titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Three-Month Ocular and Systemic Toxicity Study with a One Month Recovery Period in New Zealand White Rabbits" . . . . .	18	303
PK-95-060 Quantitation of Cyclosporin A in Rabbit Blood by Liquid Chromatography/Mass Spectrometry/Mass Spectrometry for Study 1793-2936-6, "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Six-Month Ocular and Systemic Toxicity Study with a Two Month Recovery Period in New Zealand White Rabbits" . . . . .	18	320

PK-95-066 Pharmacokinetic Analysis of Cyclosporin A in Rabbit Blood for Study No. 1793-2936-6 Titled "AGN 192371-Cyclosporine Ophthalmic Emulsion: A Six-Month Ocular and Systemic Toxicity Study with a Two Month Recovery Period in New Zealand White Rabbits" . . . . .	18	361
PK-95-073 Bioanalytical Assay Validation for Quantitating Cyclosporin A in Whole Dog Blood Using High Performance Liquid Chromatography-Tandem Mass Spectrometry . . . . .	18	381
PK-95-074 The Effect of Oil Globule Size on Ocular Absorption of 3H-Cyclosporine after Topical Instillation of Three 0.2% 3H-Cyclosporine Oil-in-Water Emulsions into Albino Rabbit Eyes. . . . .	19	001
PK-96-001 A Six-Month Interim Toxicokinetic Report: Pharmacokinetics Analysis of Cyclosporin A in Dog Blood for Study No. 985-126 Titled "52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period". . . . .	19	027
PK-96-004 Bioanalytical Assay Validation for Quantitating Cyclosporin A in Human Blood Using High Performance Liquid Chromatography-Tandem Mass Spectrometry . . . . .	19	044
PK-96-011 Dose Proportionality of Ocular Tissue 3H-Cyclosporine Concentrations after a Single Dose Administration of 0.05%, 0.2%, and 0.4% 3H-Cyclosporine Emulsions into Rabbit Eyes . . . . .	19	075
PK-96-016 3H-Cyclosporine Ocular Absorption and Disposition in Beagle Dogs Following Multiple Ocular Doses of 0.2% 3H-Cyclosporine Emulsio . . . . .	19	100
PK-96-017 3H-Cyclosporine Ocular Absorption and Disposition in Beagle Dogs Following Single Ocular Doses of 0.2% 3H-Cyclosporine Emulsion . . . . .	19	194
PK-96-018 Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca" . . . . .	19	284
PK-96-023 Twelve-Month Toxicokinetic Report: Pharmacokinetic Analysis of Cyclosporin A in Dog Blood for Study No. HWA 985-126 Titled "52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period" . . . . .	19	298
PK-98-074 Ocular Cyclosporine Distribution During 9 1/2 Days of Dosing of 0.05 and 0.1% 3H-Cyclosporin A Emulsions to Albino Rabbit Eyes . . . . .	19	327
PK-98-109 Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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" . . . . .	19	357



PK-98-112 Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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" . . . . .	19	371
Container/Closure Extractable Studies, IND Amendment Serial 097 . . . . .	20	001
IND Amendment Serial 103 . . . . .	20	069
Study Report 192731-001. . . . .	20	143
Study Report 192731-002. . . . .	20	239
SYNOPSIS . . . . .	20	257
1. STUDY IDENTIFICATION. . . . .	20	264
2. INTRODUCTION. . . . .	20	266
3. OBJECTIVE . . . . .	20	267
4. INVESTIGATIONAL PLAN . . . . .	20	268
5. GENERAL STUDY POPULATION RESULTS . . . . .	20	297
6. RESULTS OF EFFICACY ANALYSIS. . . . .	20	302
7. PHARMACOKINETIC RESULTS . . . . .	20	320
8. RESULTS OF SAFETY ANALYSIS. . . . .	20	321
9. DISCUSSION . . . . .	20	332
10. CONCLUSIONS. . . . .	20	334
11. STUDY REPORT REFERENCES . . . . .	20	336
12. LITERATURE REFERENCES. . . . .	20	337
Study Report 192731-003. . . . .	20	342
SYNOPSIS . . . . .	20	359
1. STUDY IDENTIFICATION. . . . .	20	364
2. INTRODUCTION. . . . .	20	368
3. OBJECTIVE . . . . .	20	369
4. INVESTIGATIONAL PLAN . . . . .	20	370
5. GENERAL STUDY POPULATION RESULTS . . . . .	20	398
6. RESULTS OF EFFICACY ANALYSIS. . . . .	20	403
7. PHARMACOKINETIC RESULTS . . . . .	20	416
8. RESULTS OF SAFETY ANALYSIS. . . . .	20	416
9. DISCUSSION . . . . .	20	429
10. CONCLUSIONS. . . . .	20	431
11. STUDY REPORT REFERENCES . . . . .	20	433

12. LITERATURE REFERENCES.....	20	434
5.12 NONCLINICAL LITERATURE.....	21	001
Anichini 1997.....	21	001
Bacman 1998.....	21	005
Borel 1996.....	21	011
Boss 1998.....	21	143
Bottazzo1983.....	21	152
Bottazzo 1986.....	21	157
Chawla 1996.....	21	190
Elder 1995.....	21	196
Erkko 1997.....	21	207
Evans 1993.....	21	214
Filardo 1996.....	21	223
Fox 1994.....	21	231
Gao 1998.....	21	239
Ghalie 1990.....	21	249
Goral 1997.....	21	252
Johnson 1992.....	21	261
Jones 1994.....	21	267
Kahan 1989.....	21	279
Kaswan 1985.....	21	293
Kaswan 1989.....	21	301
Kaswan 1990.....	21	308
Kaswan 1994.....	21	339
Keller 1996.....	22	001
Lacroix 1991.....	22	010
PDR-NEORAL 1998.....	22	016
Luhtala 1991.....	22	045
Lundberg 1991.....	22	051
Mamalis 1996.....	22	059
Meggs 1993.....	22	061
Memon 1995.....	22	066
Meyer 1997.....	22	070
Mircheff 1994.....	22	075
Mircheff 1996.....	22	084
Mitruka 1998.....	22	112

Mosmann 1989 .....	22	122
Nikkinen 1984 .....	22	151
Nussbaum 1995 .....	22	156
Oran 1997 .....	22	159
PDR-NEORAL 1998 .....	22	167
Pepose 1990 .....	22	196
Pette 1997 .....	22	203
Pflugfelder 1986 .....	22	212
Pflugfelder 1998a .....	22	217
Pflugfelder 1998b .....	22	224
Robinson 1998 .....	22	243
Romagnani 1991 .....	22	250
Romagnani 1996 .....	22	252
Schafer 1994 .....	22	263
Schliephake 1997 .....	22	268
Scorrano 1997 .....	22	272
Seder 1997 .....	22	276
Seidman 1991 .....	22	280
Stern 1998 .....	22	294
Sullivan 1997 .....	22	300
Sullivan 1998 .....	22	316
Svecova 1998 .....	22	321
van der Pouw Kraan 1996 .....	22	327
Walcott 1998 .....	22	333
Wang 1996 .....	22	340
Wenger 1988 .....	22	344
<b>Section 6 HUMAN PHARMACOKINETIC DATA .....</b>	<b>23</b>	<b>004</b>
6.1 OVERVIEW .....	23	004
6.1.1 SYSTEMIC EXPOSURE AFTER OPHTHALMIC ADMINISTRATION TO HUMANS .....	23	005
Table 6.1.1-1. Comparison of dose and subsequent mean blood C <sub>max</sub> , Coverage, C <sub>min</sub> , and AUC <sub>0-12</sub> between systemic therapeutic use of NEORAL® and topical use of 0.05% and 0.1% cyclosporine emulsions. ....	23	007
6.1.2 OCULAR PHARMACOKINETICS AFTER OPHTHALMIC ADMINISTRATION .....	23	007
Ocular Metabolism (reproduced from Section 5.6.1.1) .....	23	008

Ocular Absorption, Distribution, and Elimination (reproduced from Section 5.6.1.1).....	23	008
6.2 TABULAR SUMMARY .....	23	010
6.2.1 TABULAR SUMMARY OF SYSTEMIC PHARMACOKINETICS IN HUMANS.....	23	010
Table 6.2.1-1 Pharmacokinetic analysis of cyclosporin A in human blood for clinical study 192371-001 entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca.....	23	010
Table 6.2.1-2 Six month interim pharmacokinetic analysis of cyclosporin A in human blood for clinical study 192371-002 entitled "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.....	23	011
Table 6.2.1-3 Interim report of blood cyclosporin A concentrations during one dosing interval for study 192371-002 titled, "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." .....	23	012
6.3 INDIVIDUAL STUDY SUMMARIES .....	23	013
6.3.1 BIOANALYTICAL METHOD .....	23	013
6.3.2 SYSTEMIC PHARMACOKINETICS AFTER OPHTHALMIC ADMINISTRATION TO HUMANS .....	23	013
Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca" (Allergan Report PK-96-018).....	23	013
Table 6.3.2-1 Trough and maximum concentrations of cyclosporin A in human blood after ophthalmic administration of 0.05, 0.1, 0.2 or 0.4% cyclosporine emulsion twice-daily to each eye for 12 weeks.....	23	014
Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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." (Allergan Report PK-98-109).....	23	014

Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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." (Allergan Report PK-98-112). . . . .	23	015
6.4 INTEGRATED TABULAR SUMMARY . . . . .	23	017
Table 6.4-1 Blood cyclosporine concentrations after topical instillation of 0.05-0.4% 3H-cyclosporine emulsions to humans. . . . .	23	017
6.5 FORMULATIONS USED IN CLINICAL STUDIES . . . . .	23	022
Table 6.5-1 Formulations Used in Clinical Studies . . . . .	23	022
6.6 HUMAN PHARMACOKINETICS REFERENCES . . . . .	23	023
6.6.1 HUMAN PHARMACOKINETICS STUDY REPORT REFERENCES . . . . .	23	023
6.6.2 HUMAN PHARMACOKINETICS LITERATURE REFERENCES . . . . .	23	024
6.7 REFERENCES . . . . .	23	025
6.7.1 HUMAN PHARMACOKINETICS STUDY REPORTS . . . . .	23	025
PK-94-108 The Blood-to-Plasma Concentration Ratio of 3H-Cyclosporin-A in Mouse, Rat, Rabbit, Dog and Human in Vitro	23	025
PK-96-004 Bioanalytical Assay Validation for Quantitating Cyclosporin A in Human Blood Using High Performance Liquid Chromatography-Tandem Mass Spectrometry. . . . .	23	035
PK-96-018 Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca". . . . .	23	066
PK-98-109 Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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" . . . . .	23	080
PK-98-112 Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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" . . . . .	23	094
6.7.2 HUMAN PHARMACOKINETICS LITERATURE. . . . .	23	107
Elder 1995 . . . . .	23	107

Chawla 1996 .....	23	118
Erkko 1997.....	23	124
PDR-NEORAL 1998.....	23	131
<b>Section 7 MICROBIOLOGY .....</b>	<b>24</b>	<b>001</b>
<b>Section 8 CLINICAL DATA.....</b>	<b>25</b>	<b>014</b>
8.1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS .....	25	014
8.2 INVESTIGATORS, INDS AND NDAS.....	25	018
8.2.1 LIST OF INVESTIGATORS .....	25	018
Table 8.2.1 Investigator List .....	25	018
8.2.2 CURRICULA VITAE OF INVESTIGATORS .....	25	023
8.2.3 LIST OF INDS AND NDAS.....	25	024
Table 8.2.3 List of INDS and NDAs .....	25	024
8.2.4 UNEXPLAINED OMISSION OF ANY REPORTS .....	25	024
8.3 BACKGROUND AND OVERVIEW.....	25	025
8.3.1 INTRODUCTION.....	25	025
8.3.2 KERATOCONJUNCTIVITIS SICCA .....	25	025
8.3.3 TREATMENTS FOR KERATOCONJUNCTIVITIS SICCA....	25	027
8.3.3.1 Pharmacotherapy .....	25	027
8.3.3.2 Devices .....	25	027
8.3.3.3 Surgery.....	25	028
8.3.4 RATIONALE FOR USING CYCLOSPORINE OPHTHALMIC EMULSION TO TREAT KERATOCONJUNCTIVITIS SICCA .....	25	028
8.3.5 PREVIOUS CLINICAL STUDIES SUPPORTING THE EVALUATION OF TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF KERATOCONJUNCTIVITIS SICCA..	25	030
8.3.5.1 Four-Week Efficacy Study in KCS Patients With or Without Sjögren's Syndrome .....	25	030
8.3.5.2 Eight-Week Efficacy Study in Patients with KCS Associated with Sjögren's Syndrome .....	25	031
8.3.5.3 Twelve-Week Efficacy Study in KCS Patients .....	25	031
8.3.5.4 Safety and Tolerability of Sandimmune 2.0% Ophthalmic Ointment in Normal Volunteers.....	25	032
8.3.5.5 Two-Month Study of Topical Cyclosporine in Patients with Secondary Sjögren's Syndrome .....	25	033
8.3.5.6 Six-Week Safety Study of Topical Cyclosporine in Patients with Secondary Sjögren's Syndrome .....	25	033

8.3.6 PREVIOUS CLINICAL STUDIES SUPPORTING THE USE OF PHARMACY-COMPOUNDED TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF OTHER OCULAR CONDITIONS . . . . .	25	033
8.3.7 BASIS FOR THE DESIGN OF THE CLINICAL TRIALS . . . . .	25	034
8.3.7.1 Dosage . . . . .	25	034
8.3.7.2 Patient Selection Criteria . . . . .	25	035
8.3.7.3 Duration of Studies . . . . .	25	035
8.3.7.4 Timing of Visits . . . . .	25	036
8.3.7.5 Number of Patients . . . . .	25	036
8.3.7.6 Choice of Control . . . . .	25	036
8.3.7.7 Selection of Major Clinical Efficacy Endpoints . . . . .	25	036
Objective Tests . . . . .	25	037
Subjective Tests . . . . .	25	039
Tertiary Tests . . . . .	25	040
Pharmacokinetics, Laboratory, and Safety Tests . . . . .	25	041
8.3.8 DRUG CLASS AND GENERAL CONSIDERATIONS . . . . .	25	042
8.3.9 FDA/SPONSOR DISCUSSIONS . . . . .	25	042
8.3.10 SELECTION OF SPECIAL INTEREST AREAS . . . . .	25	043
8.3.11 CONCLUSIONS . . . . .	25	043
8.3.12 REFERENCES . . . . .	25	044
8.3.12.1 Study Report References . . . . .	25	044
8.3.12.2 Literature References . . . . .	25	046
8.4 CLINICAL PHARMACOLOGY . . . . .	25	052
8.4.1 INTRODUCTION . . . . .	25	052
8.4.2 ASSESSMENT OF IMMUNE ACTIVATION AND INFLAMMATORY RESPONSE . . . . .	25	052
8.4.3 OCULAR SURFACE INFLAMMATION . . . . .	25	053
8.4.4 PHARMACOLOGIC ACTIVITY . . . . .	25	054
8.4.4.1 Immunomodulation . . . . .	25	055
8.4.4.2 Anti—Inflammatory Activity . . . . .	25	055
8.4.4.3 Modulation of Pathological Apoptosis . . . . .	25	056
8.4.5 CONCLUSIONS . . . . .	25	056
8.4.6 REFERENCES . . . . .	25	056
8.5 LISTING OF INDIVIDUAL STUDY SYNOPSES . . . . .	25	059
8.5.1 OVERVIEW . . . . .	25	059
8.5.2 PHASE 2 CLINICAL STUDY . . . . .	25	060

Table 8.5.2 Phase 2 Clinical Study 192371-001 .....	25	060
8.5.3 PHASE 3 CLINICAL STUDIES .....	25	061
Table 8.5.3-1 Phase 3 Clinical Study 192371-002 .....	25	061
Table 8.5.3-2 Phase 3 Clinical Study 192371-003 .....	25	062
8.6 INTEGRATED SUMMARY OF EFFICACY .....	25	063
8.6.1 INTRODUCTION .....	25	063
8.6.2 ROLE OF THE PHASE 2 STUDY IN DETERMINING PHASE 3 STUDY DESIGN .....	25	063
8.6.3 PHASE 3 STUDY DESIGN AND PATIENT POPULATION ...	25	065
8.6.4 INTENT-TO-TREAT ANALYSIS OF EFFICACY RESULTS ..	25	066
8.6.4.1 Objective Efficacy Measures .....	25	066
Corneal Staining .....	25	066
Table 8.6.4.1—1 Corneal Fluorescein Staining in Phase 3 Studies (Intent-to-Treat Population) .....	25	067
Schirmer Tear Test with Anesthesia .....	25	068
Table 8.6.4.1-2 Categorized Schirmer Values With Anesthesia in Phase 3 Studies (Intent-to-Treat Population) .....	25	068
8.6.4.2 Subjective Efficacy Measures .....	25	069
Blurred Vision .....	25	069
Table 8.6.4.2-1 Blurred Vision in Phase 3 Studies (Intent-to-Treat Population) .....	25	069
REFRESH Use .....	25	070
Table 8.6.4.2—2 Daily REFRESH® Use During the Previous Week in Phase 3 Studies (Intent-to-Treat Population) .....	25	070
8.6.4.3 Responder Analysis .....	25	071
Table 8.6.4.3 Number and Percent of Responders in Phase 3 Studies (Intent-to-Treat Population) .....	25	072
8.6.5 META-ANALYSIS .....	25	072
Table 8.6.5 Statistically Significant Among-Group Differences in the Meta-Analysis of Phase 3 Studies (Intent-to-Treat Population) .....	25	073
8.6.6 SUBGROUP ANALYSES .....	25	073
8.6.6.1 Patients with Severe Disease .....	25	074
Table 8.6.6.1 Statistically Significant Among-Group Differences in the Severe Subgroup of the Phase 3 Studies .....	25	075
8.6.6.2 Per-Protocol Analysis .....	25	075
Table 8.6.6.2 Statistically Significant Among-Group Differences in Per-Protocol Analysis of the Phase 3 Studies .....	25	076
8.6.6.3 Sjögren’s Syndrome .....	25	077



Table 8.6.6.3 Statistically Significant Among-Group Differences in Patients with Sjögren’s Syndrome in the Phase 3 Studies. . . . .	25	078
8.6.6.4 Other Subgroups . . . . .	25	078
8.6.7 TERTIARY OPHTHALMIC TESTS: EFFECTS OF CYCLOSPORINE EMULSION ON INFLAMMATORY AND IMMUNE MECHANISMS UNDERLYING KCS. . . . .	25	079
8.6.7.1 Baseline Data for Inflammation, Immune Reactivity, and Apoptosis in KCS Patients . . . . .	25	079
Inflammation. . . . .	25	079
Immune Reactivity . . . . .	25	080
Pathological Apoptosis . . . . .	25	080
8.6.7.2 Markers of Inflammation and Immune Reactivity and Goblet Cell Density after 6 Months of Treatment with 0.05% Cyclosporine Ophthalmic Emulsion. . . . .	25	081
Inflammatory Cytokine IL—6 Levels. . . . .	25	081
Table 8.6.7.2—1 Normalized IL-6: Baseline Data and Change from Baseline at Months 3 and 6 . . . . .	25	081
Lymphocytic and Immune Activation Markers from Conjunctival Biopsies . . . . .	25	082
Table 8.6.7.2—2 Lymphocytic and Immune-Activation Markers: Baseline Data and Percent Change at Month 6. . . . .	25	083
Goblet Cell Density from Conjunctival Biopsies . . . . .	25	084
Table 8.6.7.2—3 PAS/Goblet Cell Density from Conjunctival Biopsy: Baseline Data and Percent Change at Month 6. . . . .	25	084
8.6.8 PREVIOUS CLINICAL STUDIES SUPPORTING THE EVALUATION OF TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF KERATOCONJUNCTIVITIS SICCA. . . . .	25	085
8.6.9 EVIDENCE OF LONG—TERM EFFECTIVENESS, TOLERANCE, AND WITHDRAWAL EFFECTS . . . . .	25	085
8.6.10 DOSE AND REGIMEN RATIONALE . . . . .	25	086
8.6.11 DISCUSSION AND CONCLUSIONS. . . . .	25	086
8.6.11.1 Discussion . . . . .	25	086
8.6.11.2 Conclusions . . . . .	25	089
8.6.12 REFERENCES . . . . .	25	091
8.6.12.1 Study Report References . . . . .	25	091
8.6.12.2 Literature References. . . . .	25	093
8.6.13 TABLES OF PHASE 3 STUDIES POOLED (META-ANALYSIS) . . . . .	25	095
Tables of Phase 3 Studies Pooled . . . . .	25	097
8.6.14 FIGURES. . . . .	25	148

Figure 1 Study 002, ITT: Corneal Staining, Change from Baseline . 25	149
Figure 2 Study 002, ITT: Schirmer Values (with Anesthesia), Change from Baseline. .... 25	150
Figure 3 Study 002, ITT: Blurred Vision Severity, Change from Baseline. .... 25	151
Figure 4 Study 002, ITT: Average Daily REFRESH Use During the Previous Week, Change from Baseline ..... 25	152
Figure 5 Study 003, ITT: Corneal Staining, Change from Baseline . 25	153
Figure 6 Study 003, ITT: Schirmer Values (with Anesthesia), Change from Baseline. .... 25	154
Figure 7 Study 003, ITT: Blurred Vision Severity, Change from Baseline. .... 25	155
Figure 8 Study 003, ITT: Average Daily REFRESH Use During the Previous Week, Change from Baseline ..... 25	156
Figure 9 Meta-Analysis: Corneal Staining, Change from Baseline .. 25	157
Figure 10 Meta-Analysis: Schirmer Values (with Anesthesia), Change from Baseline. .... 25	158
Figure 11 Meta-Analysis: Blurred Vision Severity, Change from Baseline. .... 25	159
Figure 12 Meta-Analysis: Average Daily REFRESH Use During the Previous Week, Change from Baseline ..... 25	160
Figure 13 Study 002, Severe Subgroup: Corneal Staining, Change from Baseline ..... 25	161
Figure 14 Study 002, Severe Subgroup: Schirmer Values (with Anesthesia), Change from Baseline ..... 25	162
Figure 15 Study 002, Severe Subgroup: Blurred Vision Severity, Change from Baseline. .... 25	163
Figure 16 Study 002, Severe Subgroup: Average Daily REFRESH Use During the Previous Week, Change from Baseline. .... 25	164
Figure 17 Study 003, Severe Subgroup: Corneal Staining, Change from Baseline ..... 25	165
Figure 18 Study 003, Severe Subgroup: Schirmer Values (with Anesthesia), Change from Baseline ..... 25	166
Figure 19 Study 003, Severe Subgroup: Blurred Vision Severity, Change from Baseline. .... 25	167
Figure 20 Study 003, Severe Subgroup: Average Daily REFRESH Use During the Previous Week, Change from Baseline. .... 25	168
8.7 INTEGRATED SUMMARY OF SAFETY ..... 26	001
8.7.1 INTRODUCTION ..... 26	001
8.7.2 TABULAR SUMMARY OF ALL STUDIES ..... 26	002

Table 8.7.2—1 Phase 2 Controlled Clinical Trial of Cyclosporine Ophthalmic Emulsion . . . . .	26	003
Table 8.7.2—2 Phase 3 Controlled Studies of Cyclosporine Ophthalmic Emulsion . . . . .	26	004
Table 8.7.2—2 Phase 3 Controlled Studies of Cyclosporine Ophthalmic Emulsion (continued) . . . . .	26	005
8.7.3 OVERALL EXTENT OF EXPOSURE . . . . .	26	006
8.7.3.1 Number of Patients Exposed Overall and for Specified Periods of Time . . . . .	26	006
8.7.3.2 Number of Patients Exposed to Various Doses for Defined Periods . . . . .	26	006
8.7.4 DEMOGRAPHIC AND OTHER CHARACTERISTICS OF STUDY POPULATIONS . . . . .	26	007
8.7.5 ADVERSE EXPERIENCES IN PHASE 3 STUDIES . . . . .	26	008
8.7.5.1 Overall Summary of Adverse Events in Phase 3 Studies . . . . .	26	008
8.7.5.2 Background Summarizing Adverse Events with Systemic Cyclosporine . . . . .	26	009
8.7.5.3 All Adverse Events Regardless of Causality in Phase 3 Studies . . . . .	26	010
Table 8.7.5.3—1 Number (%) of Patients in the Phase 3 Studies with Adverse Events by Relationship to Study Medication and Severity . . . . .	26	011
8.7.5.3-2 Number (%) of Patients in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	012
Table 8.7.5.3—3 Number (%) of Patients in the Phase 3 Studies with Adverse Events Reported by 3% of Patients in Either Cyclosporine Group, Regardless of Causality . . . . .	26	013
8.7.5.4 Treatment—Related Adverse Events in Phase 3 Studies . . . . .	26	015
Table 8.7.5.4 Number (%) of Patients in the Phase 3 Studies with Treatment-Related Adverse Events Reported by 3% of Patients in Either Cyclosporine Group . . . . .	26	016
8.7.5.5 Treatment—Unrelated Adverse Events in Phase 3 Studies . . . . .	26	016
Table 8.7.5.5 Number (%) of Patients in the Phase 3 Studies with Treatment-Unrelated Adverse Events Reported by 3% of Patients in Either Cyclosporine Group . . . . .	26	017
8.7.5.6 Serious Adverse Events in Phase 3 Studies . . . . .	26	017
8.7.5.7 Discontinuations Due to Adverse Events in Phase 3 Studies . . . . .	26	018
8.7.6 OTHER SAFETY VARIABLES IN PHASE 3 STUDIES . . . . .	26	018
8.7.6.1 Visual Acuity in Phase 3 Studies . . . . .	26	018
8.7.6.2 Intraocular Pressure in Phase 3 Studies . . . . .	26	019
8.7.6.3 Biomicroscopy in Phase 3 Studies . . . . .	26	019

8.7.6.4 Pharmacokinetics in Phase 3 Studies . . . . .	26	020
<b>8.7.7 SUMMARY OF RESULTS FROM PHASE 2 STUDY . . . . .</b>	<b>26</b>	<b>021</b>
8.7.7.1 Adverse Events in Phase 2 Study . . . . .	26	021
Table 8.7.7.1—1 Number (%) of Patients in Phase 2 Study with Adverse Events, Regardless of Causality . . . . .	26	022
Table 8.7.7.1—2 Number (%) of Patients in Phase 2 Study with Treatment—Related Adverse Events . . . . .	26	023
8.7.7.2 Formulation Tolerability in Phase 2 Study . . . . .	26	023
8.7.7.3 Serious Adverse Events and Premature Terminations in Phase 2 Study . . . . .	26	023
8.7.7.4 Blood Chemistry and Hematology in Phase 2 Study . . . . .	26	024
Table 8.7.7.4 Isolated Clinical Laboratory Abnormalities in Phase 2 Study . . . . .	26	025
8.7.7.5 Ocular Microbiology in Phase 2 Study . . . . .	26	026
Table 8.7.7.5—1 Number (%) of Patients in Phase 2 Study with Most Frequently Reported Organisms . . . . .	26	026
Table 8.7.7.5—2 Number (%) of Patients in Phase 2 Study with Organisms Isolated . . . . .	26	027
Table 8.7.7.5—3 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora after 12 Weeks of Treatment . . . . .	26	028
Table 8.7.7.5—4 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora 4 Weeks Post-Treatment . . . . .	26	028
8.7.7.6 Other Safety Variables in Phase 2 Study . . . . .	26	028
8.7.7.7 Pharmacokinetics in Phase 2 Study . . . . .	26	029
<b>8.7.8 DRUG-DRUG INTERACTIONS . . . . .</b>	<b>26</b>	<b>030</b>
<b>8.7.9 DRUG-DEMOGRAPHIC AND DRUG-DISEASE INTERACTIONS . . . . .</b>	<b>26</b>	<b>030</b>
8.7.9.1 Adverse Events by Age Group . . . . .	26	030
Table 8.7.9.1-1 Number (%) of Patients by Age Subgroup in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	031
Table 8.7.9.1-2 Number (%) of Patients by Age Subgroup with the Most Frequently Reported Body as a Whole Adverse Events in the Phase 3 Studies . . . . .	26	032
8.7.9.2 Adverse Events by Sex . . . . .	26	032
Table 8.7.9.2-1 Number (%) of Males and Females in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	033
Table 8.7.9.2-2 Number (%) of Males and Females in the Phase 3 Studies with Adverse Events Overall, in Body as a Whole, and in Skin by Treatment Group . . . . .	26	034
8.7.9.3 Adverse Events by Race . . . . .	26	034

Table 8.7.9.3 Number (%) of Caucasian/Hispanic and Non—Caucasian Patients in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	035
8.7.9.4 Adverse Events by Diagnosis . . . . .	26	036
Table 8.7.9.4 Number (%) of Sjögren’s Syndrome and Non—Sjögren’s Patients in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	037
8.7.9.5 Adverse Events by Iris Color. . . . .	26	038
Table 8.7.9.5 Number (%) of Patients with Dark Irides and Light Irides in the Phase 3 Studies with Adverse Events by Body System . . . . .	26	038
8.7.10 LONG-TERM ADVERSE EFFECTS. . . . .	26	038
8.7.11 WITHDRAWAL EFFECTS . . . . .	26	039
8.7.12 PREVIOUS HUMAN USE OF OTHER FORMULATIONS OF TOPICAL OPHTHALMIC CYCLOSPORINE . . . . .	26	039
8.7.12.1 Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Keratoconjunctivitis Sicca . . . . .	26	039
8.7.12.2 Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Other Indications . . . . .	26	041
8.7.13 SUMMARY OF RESULTS FROM IN-HOUSE ANIMAL STUDIES. . . . .	26	042
8.7.13.1 A Three-Month Ocular and Systemic Toxicity Study with a One-Month Recovery Period in New Zealand White Rabbits . . . . .	26	042
8.7.13.2 A Six-Month Ocular and Systemic Toxicity Study with a Two-Month Recovery Period in New Zealand White Rabbits . . . . .	26	042
8.7.13.3 52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period. . . . .	26	043
8.7.13.4 Margin of Safety Based on Systemic Drug Exposure . . . . .	26	044
8.7.14 DISCUSSION AND CONCLUSIONS. . . . .	26	044
8.7.14.1 Ocular Safety . . . . .	26	044
8.7.14.2 Systemic Safety . . . . .	26	045
8.7.14.3 Conclusions . . . . .	26	046
8.7.15 REFERENCES . . . . .	26	048
8.7.15.1 Study Report References. . . . .	26	048
8.7.15.2 Literature References. . . . .	26	051
8.7.16 TABLES OF PHASE 3 STUDIES POOLED . . . . .	26	055
Tables. . . . .	26	057
8.8 OTHER STUDIES AND INFORMATION . . . . .	26	309
8.8.1 OVERVIEW . . . . .	26	309
8.8.2 ONGOING CONTROLLED CLINICAL STUDIES . . . . .	26	310

Table 8.8.2.-1 Controlled Clinical Study NEI 98—EI—0032 . . . . .	26	310
Table 8.8.2-2 Controlled Clinical Study 192371-501 . . . . .	26	311
8.8.3 ONGOING OPEN-LABEL CLINICAL STUDIES . . . . .	26	312
Table 8.8.3-1 Controlled Clinical Study 192371-004 . . . . .	26	312
Table 8.8.3-2 Open-Label Clinical Study 192371-005 . . . . .	26	313
8.9 DRUG ABUSE AND OVERDOSE . . . . .	26	314
8.9.1 TOPICAL AND SYSTEMIC OVERDOSAGE . . . . .	26	314
8.9.2 ANIMAL SAFETY STUDIES . . . . .	26	314
8.9.3 REFERENCES . . . . .	26	315
8.9.3.1 Study Report References . . . . .	26	315
8.9.3.2 Literature References . . . . .	26	315
8.10 INTEGRATED SUMMARY OF BENEFITS AND RISKS OF THE DRUG . . . . .	26	316
8.10.1 BENEFITS . . . . .	26	316
8.10.2 RISKS . . . . .	26	318
8.10.2.1 Ocular Safety . . . . .	26	319
8.10.2.2 Systemic Safety . . . . .	26	319
8.10.3 CONCLUSIONS . . . . .	26	320
Component . . . . .	26	322
8.10.4.1 Study Report References . . . . .	26	322
8.10.4.2 Literature References . . . . .	26	324
8.11 CLINICAL STUDY REPORTS . . . . .	27	001
8.11.1 STUDY REPORT 192371-001 . . . . .	27	002
192731-001 Study Report, continued . . . . .	27	050
ATTACHMENT 9.0 . . . . .	27	098
ATTACHMENT 9.1 Tables . . . . .	27	099
Tables 1 to 36.1 . . . . .	27	100
Tables 36.1a to 56 . . . . .	27	149
Tables 57 to 77.2 . . . . .	27	199
Tables 77.3 to 80 . . . . .	27	248
ATTACHMENT 9.2 Tear Protein Report . . . . .	27	278
ATTACHMENT 9.3 Pharmacokinetics Report . . . . .	27	281
PK-96-018 Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study 192731-001 . . . . .	27	282
ATTACHMENT 10.0 APPENDICES . . . . .	27	296
ATTACHMENT 10.1 Protocol and Amendments . . . . .	27	297

Protocol 192731-001 .....	27	298
ATTACHMENT 10.2 Randomization Number by Investigator ..	28	001
Randomization Numbers .....	28	002
ATTACHMENT 10.3 Investigators' CV and Statement of Investigator Forms (FDA 1572, HPB 3005) .....	28	012
PRINCIPAL INVESTIGATORS .....	28	013
SUBINVESTIGATORS .....	28	113
ATTACHMENT 10.4 List of All IRBs/ERCs Consulted .....	28	200
List of IRBs .....	28	201
ATTACHMENT 10.5 Sample Informed Consent Form .....	28	202
Sample Consent Form .....	28	203
ATTACHMENT 10.6 Sample Case Report Forms .....	28	211
Screening Booklet .....	28	212
Treatment Booklet .....	28	239
Subject Diary .....	28	308
ATTACHMENT 10.7 List of Patients by Test Drug Lot Number ..	28	313
ATTACHMENT 10.8 CRFs of Patients with Serious Adverse Events and Patients Discontinued Due to Adverse Events .....	28	314
ATTACHMENT 10.8.1 CRFs of Patients with Serious Adverse Events .....	28	315
ATTACHMENT 10.8.2 CRFs of Patients Discontinued Due to Adverse Events .....	28	324
ATTACHMENT 10.9 Statistical Appendices .....	29	001
ATTACHMENT 10.9.1 Secondary Efficacy Variables .....	29	001
ATTACHMENT 10.9.2 Additional Statistical Tables .....	29	004
ATTACHMENT 10.9.3 Subject Data Listings .....	30	086
ATTACHMENT 10.9.4 Computer Documentation .....	39	303
8.11.2 STUDY REPORT 192371-002 .....	40	001
SYNOPSIS .....	40	019
1. STUDY IDENTIFICATION .....	40	026
1.1 INVESTIGATOR IDENTIFICATION AND ENROLLMENT .....	40	026
Table 1.1 List of Investigators and Number of Patients Enrolled .....	40	026
Table 1.1 List of Investigators and Number of Patients Enrolled (continued) .....	40	027
2. INTRODUCTION .....	40	028
3. OBJECTIVE .....	40	029

3.1 OBJECTIVES.....	40	029
3.2 CLINICAL HYPOTHESIS .....	40	029
4. INVESTIGATIONAL PLAN .....	40	030
4.1 OVERALL STUDY DESIGN .....	40	030
4.1.1 PROTOCOL AMENDMENTS .....	40	030
4.2 PROTECTION OF HUMAN SUBJECTS .....	40	031
4.2.1 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD AND INFORMED CONSENT .....	40	031
4.2.2 COMPLIANCE WITH DECLARATION OF HELSINKI .....	40	032
4.3 SELECTION OF CONTROLS.....	40	032
4.4 PATIENT POPULATION .....	40	032
4.4.1 STUDY POPULATION CHARACTERISTICS .....	40	032
4.4.2 INCLUSION CRITERIA .....	40	032
4.4.3 EXCLUSION CRITERIA.....	40	034
4.4.4 WITHDRAWAL CRITERIA.....	40	036
4.5 STUDY TREATMENTS .....	40	037
4.5.1 STUDY TREATMENTS AND SUPPLIES.....	40	037
4.5.2 DOSE SELECTION AND TIMING .....	40	037
4.5.3 DRUG ADMINISTRATION AND STORAGE.....	40	038
4.5.4 STUDY MASKING .....	40	038
4.5.5 METHOD FOR PATIENT TREATMENT ASSIGNMENT.....	40	039
4.6 CONCOMITANT MEDICATION.....	40	040
4.6.1 PROHIBITED MEDICATIONS .....	40	040
4.6.2 PERMISSIBLE MEDICATIONS.....	40	040
4.7 MEASURES OF COMPLIANCE WITH PROTOCOL.....	40	040
4.8 RESPONSE MEASURES .....	40	041
4.8.1 EFFICACY MEASURES.....	40	041
4.8.2 PHARMACOKINETICS .....	40	043
4.8.3 SAFETY MEASURES.....	40	044
4.9 APPROPRIATENESS AND CONSISTENCY OF MEASURES .....	40	045
4.10 CRITERIA FOR EFFECTIVENESS .....	40	045
4.11 STUDY PROCEDURES .....	40	046
4.11.1 VISIT SCHEDULE AND PROCEDURES .....	40	046
4.11.2 PROCEDURES AT EACH VISIT.....	40	049



4.12 QUALITY ASSURANCE .....	40	050
4.12.1 SPONSOR'S PROCEDURES .....	40	050
4.12.2 INVESTIGATIONAL SITE PROCEDURES .....	40	051
4.12.3 CENTRAL LABORATORY .....	40	051
4.13 STATISTICAL PLANNING AND ANALYSIS .....	40	052
4.13.1 STATISTICAL HYPOTHESIS AND SIGNIFICANCE LEVELS .....	40	052
4.13.2 SAMPLE SIZE DETERMINATION .....	40	052
4.13.3 METHODS USED IN THE ANALYSIS .....	40	052
4.13.4 CHANGES FROM THE PROTOCOL .....	40	058
5. GENERAL STUDY POPULATION RESULTS .....	40	059
5.1 STUDY DURATION .....	40	059
5.2 PATIENT DISPOSITION .....	40	059
5.3 STUDY POPULATION .....	40	060
5.3.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS .....	40	060
5.3.2 AUTOANTIBODY TESTS .....	40	061
5.3.3 SECONDARY DIAGNOSES .....	40	061
5.3.4 PRIOR THERAPY .....	40	062
5.3.5 CONCOMITANT THERAPY .....	40	062
5.4 DATA SETS ANALYZED .....	40	063
5.4.1 EFFICACY .....	40	063
5.4.2 TERTIARY OPHTHALMIC TESTS .....	40	063
5.4.3 PHARMACOKINETICS .....	40	063
5.4.4 SAFETY .....	40	063
5.4.5 COMPLIANCE WITH THE PROTOCOL .....	40	063
6. RESULTS OF EFFICACY ANALYSIS .....	40	064
6.1 OVERALL SUMMARY OF EFFICACY .....	40	064
6.2 OBJECTIVE SIGNS .....	40	066
6.2.1 CORNEAL, TEMPORAL AND NASAL INTERPALPEBRAL CONJUNCTIVAL STAINING .....	40	066
6.2.2 SCHIRMER TEAR TEST .....	40	068
6.2.3 TEAR BREAK-UP TIME .....	40	070
6.3 SUBJECTIVE SYMPTOMS .....	40	070
6.3.1 OSDI© .....	40	070
6.3.2 FACIAL EXPRESSION SUBJECTIVE RATING SCALE .....	40	071

6.3.3 SYMPTOMS OF DRY EYE .....	40	071
6.3.4 INVESTIGATOR'S EVALUATION OF GLOBAL RESPONSE TO TREATMENT .....	40	073
6.3.5 TREATMENT SUCCESS .....	40	074
6.4 RESPONDER ANALYSIS .....	40	074
6.5 OTHER VARIABLES .....	40	074
6.5.1 USE OF REFRESH@ .....	40	074
6.5.2 MEIBOMIAN GLAND HEALTH .....	40	075
6.5.3 TERTIARY OPHTHALMIC TESTS .....	40	076
6.6 DRUG-DRUG INTERACTIONS .....	40	076
6.7 SUBGROUP ANALYSES .....	40	076
6.7.1 SEVERE SUBGROUP .....	40	076
6.7.2 PER PROTOCOL .....	40	078
6.7.3 SJÖGREN'S SYNDROME .....	40	080
6.7.4 OTHER SUBGROUPS .....	40	082
7. PHARMACOKINETIC RESULTS .....	40	082
8. RESULTS OF SAFETY ANALYSIS .....	40	083
8.1 OVERALL SUMMARY OF SAFETY .....	40	083
8.2 EXTENT OF EXPOSURE .....	40	084
8.3 ADVERSE EVENTS .....	40	085
8.3.1 ALL ADVERSE EVENTS REGARDLESS OF CAUSALITY .....	40	085
8.3.2 TREATMENT-RELATED ADVERSE EVENTS .....	40	088
8.3.3 TREATMENT-UNRELATED ADVERSE EVENTS .....	40	090
8.3.4 SERIOUS ADVERSE EVENTS .....	40	090
8.3.5 DISCONTINUATIONS DUE TO ADVERSE EVENTS .....	40	091
8.4 OTHER SAFETY VARIABLES .....	40	091
8.4.1 VISUAL ACUITY .....	40	091
8.4.2 INTRAOCULAR PRESSURE .....	40	092
8.4.3 BIOMICROSCOPY .....	40	093
9. DISCUSSION .....	40	094
10. CONCLUSIONS .....	40	096
11. STUDY REPORT REFERENCES .....	40	098
12. LITERATURE REFERENCES .....	40	099
13. ATTACHMENTS .....	40	104
13.1 LIST OF TABLES .....	40	104

Table 1 .....	40	108
Table 2 .....	40	109
Table 3 .....	40	111
Table 4 .....	40	117
Table 5 .....	40	119
Table 6 .....	40	126
Table 7 .....	40	127
Table 8 .....	40	128
Table 9 .....	40	157
Table 10 .....	40	176
Table 11 .....	40	178
Table 12 .....	40	180
Table 13 .....	40	192
Table 14 .....	40	197
Table 15 .....	40	200
Table 16 .....	40	220
Table 17 .....	40	231
Table 18 .....	40	233
Table 19 .....	40	234
Table 20 .....	40	236
Table 21 .....	40	239
Table 22 .....	40	241
Table 23 .....	40	242
Table 24 .....	40	243
Table 25 .....	40	245
Table 26 .....	40	247
Table 27 .....	40	249
Table 28 .....	40	250
Table 29 .....	40	251
Table 30 .....	40	258
Table 31 .....	40	285
Table 32 .....	40	287
Table 33 .....	40	293
Table 34 .....	40	299
Table 35 .....	41	001
Table 36 .....	41	097

Table 37 .....	41	098
Table 38 .....	41	106
Table 39 .....	41	116
Table 40 .....	41	117
Table 41 .....	41	132
Table 42 .....	41	133
Table 43 .....	41	134
Table 44 .....	41	142
13.2 LIST OF FIGURES .....	41	145
Figure 1 Corneal Staining (ITT) .....	41	146
Figure 2 Blurred Vision Severity (ITT).....	41	147
Figure 3 Schirmer Values (ITT).....	41	148
Figure 4 Patient Responses .....	41	149
Figure 5 Corneal Staining (Severe Subgroup).....	41	150
Figure 6 Blurred Vision Severity (Severe Subgroup) .....	41	151
Figure 7 Schirmer Values (Severe Subgroup) .....	41	152
Figure 8 Patient Responses (Severe Subgroup).....	41	153
13.3 PATIENT NARRATIVES .....	41	154
13.3.1 NARRATIVES FOR PATIENTS TREATED WITH 0.05% CYCLOSPORINE.....	41	154
13.3.2 NARRATIVES FOR PATIENTS TREATED WITH 0.1% CYCLOSPORINE.....	41	157
13.3.3 NARRATIVES FOR PATIENTS TREATED WITH VEHICLE .....	41	162
14. APPENDICES.....	41	167
14.1 PROTOCOL AND AMENDMENTS.....	41	167
Protocol192371-002-03 .....	41	168
14.2 RANDOMIZATION NUMBER BY INVESTIGATOR ....	41	268
Randomization Code .....	41	269
14.3 PRINCIPAL INVESTIGATORS' CURRICULA VITAE AND COPIES OF STATEMENT OF INVESTIGATOR FORMS 1572.....	42	001
Berdy 1572.....	42	002
Berdy CV .....	42	004
Epstein 1572.....	42	009
Epstein CV.....	42	011
Foerster 1572 .....	42	033

Foerster CV .....	42	035
Forstot 1572 .....	42	036
Forstot CV .....	42	038
Heideman 1572 .....	42	052
Heideman CV .....	42	054
Nelson 1572 .....	42	059
Nelson CV .....	42	061
O'Day 1572 .....	42	063
O'Day CV .....	42	065
Perry 1572 .....	42	069
Perry CV .....	42	071
Sall 1572 .....	42	118
Sall CV .....	42	120
Schiffman 1572 .....	42	122
Schiffman CV .....	42	124
Stevenson 1572 .....	42	130
Stevenson CV .....	42	132
Stewart 1572 .....	42	138
Stewart CV .....	42	140
Stonecipher 1572 .....	42	175
Stonecipher CV .....	42	177
Trocme 1572 .....	42	185
Trocme CV .....	42	187
14.3.1 SUBINVESTIGATOR CVs .....	42	205
14.4 LIST OF ALL IRBS CONSULTED .....	42	312
14.5 SAMPLE INFORMED CONSENT FORMS .....	42	313
14.5.1 PRESCREENING INFORMED CONSENT SAMPLE FORM .....	42	314
14.5.2 STUDY INFORMED CONSENT SAMPLE FORM .....	42	316
14.5.3 ADDITIONAL BLOOD DRAW AND TEAR COLLECTION INFORMED CONSENT SAMPLE FORM .....	42	323
14.6 SAMPLE CASE REPORT FORMS .....	43	001
Screening Log .....	43	002
Screening Exam .....	43	005
Qualification Exam .....	43	027
Concomitant Medications .....	43	047

Month 1 exam .....	43	048
Month 1 Adverse event .....	43	062
Month 1 Concomitant Medications .....	43	065
Month 1 Concurrent Procedures .....	43	066
Month 3 Exam .....	43	068
Month 4 Exam .....	43	083
Month 4 Adverse Event .....	43	097
Month 4 Concomitant Medications .....	43	100
Month 4 Concurrent Procedures .....	43	101
Month 6 Exam .....	43	103
Month 6 Adverse Event .....	43	119
Month 6 Concomitant Medications .....	43	122
Month 6 Concurrent Procedures .....	43	123
Month 6 Exit .....	43	125
Month 12 Exam .....	43	127
Month 12 Adverse Event .....	43	144
Month 12 Concomitant Medications .....	43	147
Month 12 Concurrent Procedures .....	43	148
Month 12 Exit .....	43	150
Month 12 Plus Exam .....	43	152
Month 12 Plus Adverse Event .....	43	159
Month 12 Plus Concomitant Medicaitons .....	43	162
Month 12 Plus Concurrent Procedures .....	43	163
Month 12 Plus Exit .....	43	165
Other CRFs .....	43	167
14.7 PHARMACOKINETICS REPORT .....	43	203
PK-98-109 Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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" .....	43	204
14.8 LIST OF PATIENTS BY TEST DRUG LOT NUMBER ...	43	218
Patients by Lot Number .....	43	219
14.9 CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS .....	43	231

14.10 STATISTICAL APPENDICES . . . . .	43	232
14.10.1 STATISTICAL ANALYSIS PLAN . . . . .	43	232
14.10.2 SUPPLEMENTAL STATISTICAL METHODOLOGY . . . . .	44	001
14.10.3 SUBGROUP ANALYSES . . . . .	44	048
14.10.4 PER VISIT TABLES . . . . .	45	283
14.10.5 PATIENT DATA LISTINGS . . . . .	46	001
8.11.3 STUDY REPORT 192371-003 . . . . .	60	001
SYNOPSIS . . . . .	60	018
1. STUDY IDENTIFICATION . . . . .	60	023
1.1 INVESTIGATOR IDENTIFICATION AND ENROLLMENT . . . . .	60	023
Table 1.1 List of Investigators and Number of Patients Enrolled . . . . .	60	023
Table 1.1 List of Investigators and Number of Patients Enrolled (continued) . . . . .	60	024
Table 1.1 List of Investigators and Number of Patients Enrolled (continued) . . . . .	60	025
Table 1.1 List of Investigators and Number of Patients Enrolled (continued) . . . . .	60	026
2. INTRODUCTION . . . . .	60	027
3. OBJECTIVE . . . . .	60	028
3.1 OBJECTIVES . . . . .	60	028
3.2 CLINICAL HYPOTHESIS . . . . .	60	028
4. INVESTIGATIONAL PLAN . . . . .	60	029
4.1 OVERALL STUDY DESIGN . . . . .	60	029
4.1.1 PROTOCOL AMENDMENTS . . . . .	60	029
4.2 PROTECTION OF HUMAN SUBJECTS . . . . .	60	030
4.2.1 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD AND INFORMED CONSENT . . . . .	60	030
4.2.2 COMPLIANCE WITH DECLARATION OF HELSINKI . . . . .	60	031
4.3 SELECTION OF CONTROLS . . . . .	60	031
4.4 PATIENT POPULATION . . . . .	60	031
4.4.1 STUDY POPULATION CHARACTERISTICS . . . . .	60	031
4.4.2 INCLUSION CRITERIA . . . . .	60	031
4.4.3 EXCLUSION CRITERIA . . . . .	60	033
4.4.4 WITHDRAWAL CRITERIA . . . . .	60	035

4.5 STUDY TREATMENTS .....	60	036
4.5.1 STUDY TREATMENTS AND SUPPLIES .....	60	036
4.5.2 DOSE SELECTION AND TIMING .....	60	036
4.5.3 DRUG ADMINISTRATION AND STORAGE .....	60	037
4.5.4 STUDY MASKING .....	60	037
4.5.5 METHOD FOR PATIENT TREATMENT ASSIGNMENT .....	60	038
4.6 CONCOMITANT MEDICATION .....	60	039
4.6.1 PROHIBITED MEDICATIONS .....	60	039
4.6.2 PERMISSIBLE MEDICATIONS .....	60	039
4.7 MEASURES OF COMPLIANCE WITH PROTOCOL .....	60	039
4.8 RESPONSE MEASURES .....	60	040
4.8.1 EFFICACY MEASURES .....	60	040
4.8.2 PHARMACOKINETICS NOT APPLICABLE .....	60	042
4.8.3 SAFETY MEASURES .....	60	042
4.9 APPROPRIATENESS AND CONSISTENCY OF MEASURES .....	60	044
4.10 CRITERIA FOR EFFECTIVENESS .....	60	044
4.11 STUDY PROCEDURES .....	60	044
4.11.1 VISIT SCHEDULE AND PROCEDURES .....	60	044
4.11.2 PROCEDURES AT EACH VISIT .....	60	047
4.12 QUALITY ASSURANCE .....	60	048
4.12.1 SPONSOR'S PROCEDURES .....	60	048
4.12.2 INVESTIGATIONAL SITE PROCEDURES .....	60	049
4.12.3 CENTRAL LABORATORY .....	60	049
4.13 STATISTICAL PLANNING AND ANALYSIS .....	60	049
4.13.1 STATISTICAL HYPOTHESIS AND SIGNIFICANCE LEVELS .....	60	049
4.13.2 SAMPLE SIZE DETERMINATION .....	60	050
4.13.3 METHODS USED IN THE ANALYSIS .....	60	050
4.13.4 CHANGES FROM THE PROTOCOL .....	60	056
5. GENERAL STUDY POPULATION RESULTS .....	60	057
5.1 STUDY DURATION .....	60	057
5.2 PATIENT DISPOSITION .....	60	057
5.3 STUDY POPULATION .....	60	058
5.3.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS .....	60	058



5.3.2 AUTOANTIBODY TESTS . . . . .	60	058
5.3.3 SECONDARY DIAGNOSES. . . . .	60	059
5.3.4 PRIOR THERAPY . . . . .	60	059
5.3.5 CONCOMITANT THERAPY . . . . .	60	060
5.4 DATA SETS ANALYZED . . . . .	60	060
5.4.1 EFFICACY . . . . .	60	060
5.4.2 TERTIARY OPHTHALMIC TESTS. . . . .	60	061
5.4.3 PHARMACOKINETICS NOT APPLICABLE. . . . .	60	061
5.4.4 SAFETY . . . . .	60	061
5.4.5 COMPLIANCE WITH THE PROTOCOL . . . . .	60	061
6. RESULTS OF EFFICACY ANALYSIS. . . . .	60	062
6.1 OVERALL SUMMARY OF EFFICACY . . . . .	60	062
6.2 OBJECTIVE SIGNS. . . . .	60	063
6.2.1 CORNEAL, TEMPORAL AND NASAL INTERPALPEBRAL CONJUNCTIVAL STAINING. . . . .	60	063
6.2.2 SCHIRMER TEAR TEST . . . . .	60	064
6.2.3 TEAR BREAK-UP TIME. . . . .	60	066
6.3 SUBJECTIVE SYMPTOMS . . . . .	60	066
6.3.1 OSDI®. . . . .	60	066
6.3.2 FACIAL EXPRESSION SUBJECTIVE RATING SCALE . . . . .	60	066
6.3.3 SYMPTOMS OF DRY EYE . . . . .	60	067
6.3.4 INVESTIGATOR'S EVALUATION OF GLOBAL RESPONSE TO TREATMENT. . . . .	60	067
6.3.5 TREATMENT SUCCESS . . . . .	60	068
6.4 RESPONDER ANALYSIS . . . . .	60	068
6.5 OTHER VARIABLES . . . . .	60	068
6.5.1 USE OF REFRESH®. . . . .	60	068
6.5.2 MEIBOMIAN GLAND HEALTH. . . . .	60	070
6.5.3. TERTIARY OPHTHALMIC TESTS . . . . .	60	070
6.6 DRUG-DRUG INTERACTIONS . . . . .	60	070
6.7 SUBGROUP ANALYSES . . . . .	60	071
6.7.1 SEVERE SUBGROUP. . . . .	60	071
6.7.2 PER PROTOCOL. . . . .	60	073
6.7.3 SJÖGREN'S SYNDROME . . . . .	60	074
6.7.4 OTHER SUBGROUPS. . . . .	60	075

7. PHARMACOKINETIC RESULTS .....	60	075
8. RESULTS OF SAFETY ANALYSIS.....	60	075
8.1 OVERALL SUMMARY OF SAFETY .....	60	075
8.2 EXTENT OF EXPOSURE.....	60	077
8.3 ADVERSE EVENTS .....	60	077
8.3.1 ALL ADVERSE EVENTS REGARDLESS OF CAUSALITY .....	60	077
8.3.2 TREATMENT-RELATED ADVERSE EVENTS.....	60	082
8.3.3 TREATMENT-UNRELATED ADVERSE EVENTS... ..	60	083
8.3.4 SERIOUS ADVERSE EVENTS .....	60	085
8.3.5 DISCONTINUATIONS DUE TO ADVERSE EVENTS	60	085
8.4 OTHER SAFETY VARIABLES .....	60	086
8.4.1 VISUAL ACUITY .....	60	086
8.4.2 INTRAOCULAR PRESSURE.....	60	086
8.4.3 BIOMICROSCOPY .....	60	087
9. DISCUSSION .....	60	088
10. CONCLUSIONS.....	60	090
11. STUDY REPORT REFERENCES .....	60	092
12. LITERATURE REFERENCES.....	60	093
13. ATTACHMENTS .....	60	098
13.1 LIST OF TABLES .....	60	098
Table 1 .....	60	102
Table 2 .....	60	103
Table 3 .....	60	105
Table 4 .....	60	111
Table 5 .....	60	113
Table 6 .....	60	121
Table 7 .....	60	122
Table 8 .....	60	123
Table 9 .....	60	153
Table 10 .....	60	174
Table 11 .....	60	176
Table 12 .....	60	179
Table 13 .....	60	190
Table 14 .....	60	193
Table 15 .....	60	195

Table 16 .....	60	212
Table 17 .....	60	225
Table 18 .....	60	227
Table 19 .....	60	228
Table 20 .....	60	231
Table 21 .....	60	234
Table 22 .....	60	236
Table 23 .....	60	237
Table 24 .....	60	238
Table 25 .....	60	239
Table 26 .....	60	241
Table 27 .....	60	243
Table 28 .....	60	244
Table 29 .....	60	245
Table 30 .....	60	252
Table 31 .....	60	281
Table 32 .....	60	283
Table 33 .....	60	289
Table 34 .....	60	296
Table 35 .....	61	001
Table 36 .....	61	169
Table 37 .....	61	170
Table 38 .....	61	176
Table 39 .....	61	184
Table 40 .....	61	185
Table 41 .....	61	207
Table 42 .....	61	208
Table 43 .....	61	209
Table 44 .....	61	217
<b>13.2 LIST OF FIGURES .....</b>	<b>61</b>	<b>225</b>
Figure 1 Corneal Staining (ITT) .....	61	226
Figure 2 Blurred Vision Severity (ITT).....	61	227
Figure 3 Schirmer Values (ITT).....	61	228
Figure 4 Patient Responses .....	61	229
Figure 5 Corneal Staining (Severe Subgroup).....	61	230
Figure 6 Blurred Vision Severity (Severe Subgroup).....	61	231

Figure 7 Schirmer Values (Severe Subgroup).....	61	232
Figure 8 Patient Responses (Severe Subgroup).....	61	233
13.3 PATIENT NARRATIVES .....	61	234
13.3.1 NARRATIVES FOR PATIENTS TREATED WITH 0.05% CYCLOSPORINE.....	61	234
13.3.2 NARRATIVES FOR PATIENTS TREATED WITH 0.1% CYCLOSPORINE.....	61	237
13.3.3 NARRATIVES FOR PATIENTS TREATED WITH VEHICLE .....	61	240
14. APPENDICES .....	61	242
14.1 PROTOCOL AND AMENDMENTS.....	61	242
Protocol 192371-003-02.....	61	243
14.2 RANDOMIZATION NUMBER BY INVESTIGATOR ....	61	332
Randomization Code .....	61	333
14.3 PRINCIPAL INVESTIGATORS' CURRICULA VITAE AND COPIES OF STATEMENT OF INVESTIGATOR FORMS 1572.....	62	001
Asbell 1572 .....	62	002
Asbell CV.....	62	004
Barber 1572 .....	62	049
Barber CV .....	62	051
Burke 1572.....	62	057
Burke CV .....	62	059
Cavanagh 1572.....	62	064
Cavanagh CV.....	62	066
Donshik 1572.....	62	126
Donshik CV .....	62	128
Foulks 1572 .....	62	151
Foulks CV .....	62	153
Friedlaender 1572.....	62	167
Friedlaender CV.....	62	169
Friedman 1572 .....	62	185
Friedman CV .....	62	187
Greenberg 1572 .....	62	188
Greenberg CV .....	62	190
Gruber 1572.....	62	191
Gruber CV .....	62	193

Laibovitz 1572.....	62	195
Laibovitz CV .....	62	197
Mamalis 1572.....	62	203
Mamalis CV.....	62	205
McGarey 1572.....	62	230
McGarey CV .....	62	232
Mundorf 1572.....	62	234
Mundorf CV.....	62	236
Ostrov 1572 .....	62	238
Ostrov CV .....	62	240
Pflugfelder 1572.....	62	244
Pflugfelder CV.....	62	246
Sansone 1572.....	62	271
Sansone CV .....	62	273
Schanzlin 1572.....	62	280
Schanzlin CV.....	62	282
Sheppard 1572.....	62	293
Sheppard CV .....	62	295
Stamler 1572 .....	62	301
Stamler CV.....	62	303
Tauber 1572.....	62	308
Tauber CV .....	62	310
Walters 1572 (replaced Laibovitz).....	62	315
Walters CV.....	62	317
Williams 1572 .....	62	327
Williams CV.....	62	329
Yee 1572 .....	62	333
Yee CV.....	62	335
14.3.1 SUBINVESTIGATOR CVs.....	63	001
14.4 LIST OF ALL IRBS CONSULTED.....	63	138
14.5 SAMPLE INFORMED CONSENT FORMS.....	63	140
Consent Form Prescreening.....	63	141
Consent Form.....	63	143
14.6 SAMPLE CASE REPORT FORMS.....	63	150
Screening Log .....	63	151
Screening Exam.....	63	154

Qualification Exam . . . . .	63	171
Concomitant Medications . . . . .	63	191
Month 1 Exam . . . . .	63	192
Month 1 Adverse Event . . . . .	63	205
Month 1 Concomitant Medications . . . . .	63	208
Month 1 Concurrent Procedures . . . . .	63	209
Month 3 Exam . . . . .	63	211
Month 4 Exam . . . . .	63	226
Month 4 Adverse Event . . . . .	63	240
Month 4 Concomitant Medications . . . . .	63	243
Month 4 Concurrent Procedures . . . . .	63	244
Month 6 Exam . . . . .	63	246
Month 6 Adverse Event . . . . .	63	262
Month 6 Concomitant Medications . . . . .	63	265
Month 6 Concurrent Procedures . . . . .	63	266
Month 6 Exit . . . . .	63	268
Month 12 Exam . . . . .	63	270
Month 12 Adverse Event . . . . .	63	285
Month 12 Concomitant Medications . . . . .	63	288
Month 12 Concurrent Procedures . . . . .	63	289
Month 12 Exit . . . . .	63	291
Month 12 Plus Exam . . . . .	63	293
Month 12 Plus Adverse Event . . . . .	63	300
Month 12 plus Concomitant Medications . . . . .	63	303
Month 12 Plus Concurrent Procedures . . . . .	63	304
Month 12 Plus Exit . . . . .	63	306
Other CRFs . . . . .	63	308
14.7 PHARMACOKINETICS REPORT . . . . .	64	001
14.8 LIST OF PATIENTS BY TEST DRUG LOT NUMBER . . . . .	64	002
Patient by Lot Number . . . . .	64	003
14.9 CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS . . . . .	64	013
14.10 STATISTICAL APPENDICES . . . . .	64	014
14.10.1 STATISTICAL ANALYSIS PLAN . . . . .	64	014

14.10.2 SUPPLEMENTAL STATISTICAL METHODOLOGY .....	64	184
14.10.3 SUBGROUP ANALYSES .....	64	236
14.10.4 PER VISIT TABLES .....	66	001
14.10.5 PATIENT DATA LISTINGS.....	66	044
8.11.4 INVESTIGATOR SUMMARY REPORT OF NEI 98-0032 BASELINE CONJUNCTIVAL BIOPSY .....	85	001
Signature .....	85	002
Summary Report .....	85	003
8.11.5 INVESTIGATOR SUMMARY REPORT OF BASELINE FLOW CYTOMETRY .....	85	008
Signature .....	85	009
Summary Report .....	85	010
8.11.6 INVESTIGATOR SUMMARY REPORT OF INFLAMMATORY CYTOKINE INTERLEUKIN-6 .....	85	016
Signature .....	85	017
Summary Report .....	85	018
8.11.7 INVESTIGATOR SUMMARY REPORT OF CONJUNCTIVAL BIOPSY .....	85	029
Signature .....	85	030
Summary Report .....	85	031
Figure 1.....	85	058
Figure 2.....	85	059
Figure 3.....	85	060
Figure 4.....	85	061
Photographs.....	85	062
8.11.8 INVESTIGATOR SUMMARY REPORT OF CONJUNCTIVAL GOBLET CELL DENSITY.....	85	072
Signature .....	85	073
Summary Report .....	85	074
8.11.9 INVESTIGATOR SUMMARY REPORT OF TEAR OSMOLALITY.....	85	094
Signature .....	85	095
Summary Report .....	85	096
8.11.10 OCULAR SURFACE DISEASE INDEX VALIDATION FINAL REPORT.....	85	109
OSDI Appendix 9.1 Protocol.....	85	152
OSDI Appendix 9.2 Sample Case Report Forms .....	85	187

OSDI Appendix 9.3 References. . . . .	85	213
8.11.11 K-201 STUDY REPORT SYNOPSIS: A single-center, double-masked clinical trial to assess safety, ocular tolerability, and initial efficacy of three doses of Sandimmune® ophthalmic ointment in the treatment of vernal keratoconjunctivitis and keratoconjunctivitis sicca. Sandoz 1994. . . . .	85	265
8.11.12 K-203 ALLERGAN SUMMARY OF SANDOZ CLINICAL STUDY . . . . .	85	267
8.11.13 K-204 STUDY REPORT SYNOPSIS: A double-masked clinical trial to assess safety and efficacy of Sandimmune® 2% ophthalmic ointment vs. placebo in the prevention of graft rejection in "high risk" corneal transplantation patients. Sandoz 1994. . . . .	85	297
8.11.14 K-206 ALLERGAN SUMMARY OF SANDOZ CLINICAL STUDY . . . . .	85	302
8.11.15 K-301 STUDY REPORT SYNOPSIS: A randomized double-masked clinical trial to assess the safety and efficacy of Sandimmune® 2% ophthalmic ointment vs. placebo in the prevention of graft rejection in "high risk" corneal transplantation patients. Sandoz 1994. . . . .	85	321
8.11.16 PK-95-010 Ocular Pharmacokinetics of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes . . . . .	85	334
8.11.17 PK-96-018 Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca". . . . .	85	366
8.11.18 PK-98-109 Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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". . . . .	85	380
8.11.19 PK-98-112 Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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". . . . .	85	394
8.12 CLINICAL LITERATURE. . . . .	86	001
Adamson 1983 . . . . .	86	001
Aragona 1987 . . . . .	86	007
Baudouin 1992 . . . . .	86	015



Baudouin 1997 .....	86	020
Belin 1989.....	86	027
Belin 1990.....	86	034
BenEzra 1988.....	86	046
Berry 1990 .....	86	052
Bjerrum 1997 .....	86	056
Bleik 1991.....	86	062
Borel 1996 .....	86	068
Borel 1996 part b.....	86	131
Boss 1998 .....	86	200
Brignole 1998.....	86	209
Castillo 1994.....	86	220
Chen 1990.....	86	221
Colton 1974 .....	86	227
Conover 1980.....	86	229
Damato 1984.....	86	250
Drosos 1986 .....	86	257
Dustin 1988.....	86	261
Farris 1983 .....	86	272
Florio 1996 .....	86	278
Foulks 1996 .....	86	288
Fox 1986.....	86	289
Fujihara 1997 .....	86	296
Gao 1998.....	86	303
Ghalie 1990.....	86	313
Gilbard 1978.....	86	316
Gilbard 1986.....	86	321
Gilbard 1994.....	86	334
Gipson 1997 .....	86	344
Goichot 1988 .....	86	362
Griffiths 1990.....	87	001
Gunduz 1993.....	87	007
Gunduz 1994.....	87	012
Gunduz 1997.....	87	017
Helms 1996.....	87	021
Hess 1993 .....	87	022

Hikichi 1995 .....	87	031
Hodgkin 1987 .....	87	035
Hoffmann 1985 .....	87	043
Hoffmann 1985/1986 .....	87	048
Holland 1993 .....	87	053
Holly 1977 .....	87	060
Iacono 1997 .....	87	079
Ippolito 1993 .....	87	088
Jabs 1988 .....	87	099
Janeway 1994 .....	87	106
Jones 1994 .....	87	115
Kahan 1983 .....	87	127
Kahan 1989 .....	87	137
Kahan 1994 .....	87	151
Kaswan 1989 .....	87	163
Kaswan 1990 .....	87	170
Kaswan 1994 .....	87	201
Kervick 1992 .....	87	213
Kronbach 1988 .....	87	222
Laibovitz 1993 .....	87	228
Lemp 1995 .....	87	237
Lemp 1997 .....	87	249
Lubniewski 1990 .....	87	262
Mackie 1984 .....	87	282
Mantel 1980 .....	87	286
Matsue 1995 .....	87	305
Matsumoto 1996 .....	87	311
McCarty 1998 .....	87	320
Memon 1995 .....	87	326
Meyer 1997 .....	87	330
Mircheff 1994 .....	87	335
Mitruka 1998 .....	87	344
Morgan 1991 .....	87	354
Mosmann 1989 .....	88	001
Norn 1973 .....	88	030
Nussbaum 1995 .....	88	039

Olivero 1991.....	88	042
Oran 1997.....	88	046
Ormerod 1988.....	88	054
Oyer 1983.....	88	061
Palmer 1996.....	88	068
Patel 1989.....	88	072
Pathak 1980.....	88	076
PDR-METHOTREXATE 1998.....	88	084
PDR-NEORAL 1998.....	88	103
PDR-SANDIMMUNE 1998.....	88	132
Pepose 1990.....	88	146
Pette 1997.....	88	153
Pflugfelder 1986.....	88	162
Pflugfelder 1990.....	88	167
Pflugfelder 1996.....	88	174
Pflugfelder 1997.....	88	175
Pflugfelder 1999.....	88	188
Philip 1994.....	88	220
Power 1993.....	88	224
Ralph 1975.....	88	229
Raphael 1988.....	88	233
Ren 1996.....	88	245
Romagnani 1991.....	88	254
Salisbury 1995.....	88	256
Sanders 1986.....	88	261
SAS 1996.....	88	301
Sayama 1994.....	88	306
Schein 1997.....	88	311
Schliephake 1997.....	88	317
Scorrano 1997.....	88	321
Seal 1985.....	88	325
Secchi 1990.....	88	333
Secchi 1997.....	88	338
Smith 1999.....	88	340
Solch 1991.....	88	341
Starzl 1983a.....	88	352

Starzl 1983b .....	89	001
Stern 1998.....	89	005
Sullivan 1994 .....	89	011
Sumida 1995.....	89	019
Svecova 1998 .....	89	025
Takaya 1997 .....	89	031
Tornheim 1980.....	89	036
Tseng 1985 .....	89	037
Tsubota 1991 .....	89	043
van der Pouw Kraan 1996 .....	89	046
Vitali 1993 .....	89	052
Wakefield 1992.....	89	060
White 1993 .....	89	065
Wiebking 1986.....	89	072
Williamson 1973.....	89	075
Wilson 1996a .....	89	082
Wilson 1996b .....	89	093
Zhao 1993.....	89	106
Zhao 1995.....	89	114
Zierhut 1989 .....	89	120
<b>Section 9 SAFETY UPDATE REPORT .....</b>	<b>89</b>	<b>126</b>
9.1 BACKGROUND AND INTRODUCTION .....	89	126
9.2 SAFETY FINDINGS SINCE DATALOCK.....	89	126
9.3 PATIENT NARRATIVES .....	89	128
9.3.1 NARRATIVES FOR PATIENTS TREATED WITH 0.05% CYCLOSPORINE EMULSION IN STUDIES 192371-002 AND 192371-003 .....	89	128
9.3.2 NARRATIVES FOR PATIENTS TREATED WITH 0.1% CYCLOSPORINE EMULSION IN STUDIES 192371-002 AND 192371-003 .....	89	132
9.3.3 NARRATIVES FOR PATIENTS TREATED WITH VEHICLE FOR 6 MONTHS FOLLOWED BY 0.1% CYCLOSPORINE EMULSION IN STUDIES 192371-002 AND 192371-003.....	89	134
9.3.4 NARRATIVES FOR PATIENTS TREATED WITH 0.1% CYCLOSPORINE EMULSION IN STUDY 192371-004 .....	89	137
CONCLUSION .....	89	138
<b>Section 10 STATISTICAL SECTION.....</b>	<b>90</b>	<b>010</b>
10.1 ELECTRONIC DATA .....	90	010

192371-002 AND 192371-003 PHASE 3 STUDIES	CD-ROM		
CONTENTS	.....	90	010
RAW DATASET CONTENTS	.....	90	010
WORKING DATASETS	.....	90	013
SAS PROGRAMS	.....	90	015
10.2 ANNOTATED CASE REPORT FORMS	.....	90	016
Screening	.....	90	017
Day 0	.....	90	041
Month 1	.....	90	061
Month 3	.....	90	075
Month 4	.....	90	090
Month 12	.....	90	120
Unscheduled Visit	.....	90	141
Exit Forms	.....	90	157
Other	.....	90	164
Concomitant Medications	.....	90	168
Concurrent Procedures	.....	90	180
Adverse Events	.....	90	190
10.3 CLINICAL DATA	.....	90	205
8.1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	....	90	206
8.2 INVESTIGATORS, INDS AND NDAS	.....	90	210
8.2.1 LIST OF INVESTIGATORS	.....	90	210
Table 8.2.1 Investigator List	.....	90	210
8.2.2 CURRICULA VITAE OF INVESTIGATORS	.....	90	215
8.2.3 LIST OF INDS AND NDAS	.....	90	216
Table 8.2.3 List of INDS and NDAs	.....	90	216
8.2.4 UNEXPLAINED OMISSION OF ANY REPORTS	.....	90	216
8.3 BACKGROUND AND OVERVIEW	.....	90	217
8.3.1 INTRODUCTION	.....	90	217
8.3.2 KERATOCONJUNCTIVITIS SICCA	.....	90	217
8.3.3 TREATMENTS FOR KERATOCONJUNCTIVITIS SICCA	..	90	219
8.3.3.1 Pharmacotherapy	.....	90	219
8.3.3.2 Devices	.....	90	219
8.3.3.3 Surgery	.....	90	220

8.3.4 RATIONALE FOR USING CYCLOSPORINE OPHTHALMIC EMULSION TO TREAT KERATOCONJUNCTIVITIS SICCA. ....	90	220
8.3.5 PREVIOUS CLINICAL STUDIES SUPPORTING THE EVALUATION OF TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF KERATOCONJUNCTIVITIS SICCA. ....	90	222
8.3.5.1 Four-Week Efficacy Study in KCS Patients With or Without Sjögren's Syndrome . . . . .	90	222
8.3.5.2 Eight-Week Efficacy Study in Patients with KCS Associated with Sjögren's Syndrome. . . . .	90	223
8.3.5.3 Twelve-Week Efficacy Study in KCS Patients . . . . .	90	223
8.3.5.4 Safety and Tolerability of Sandimmune 2.0% Ophthalmic Ointment in Normal Volunteers. . . . .	90	224
8.3.5.5 Two-Month Study of Topical Cyclosporine in Patients with Secondary Sjögren's Syndrome. . . . .	90	225
8.3.5.6 Six-Week Safety Study of Topical Cyclosporine in Patients with Secondary Sjögren's Syndrome . . . . .	90	225
8.3.6 PREVIOUS CLINICAL STUDIES SUPPORTING THE USE OF PHARMACY-COMPOUNDED TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF OTHER OCULAR CONDITIONS . . . . .	90	225
8.3.7 BASIS FOR THE DESIGN OF THE CLINICAL TRIALS . . .	90	226
8.3.7.1 Dosage. . . . .	90	226
8.3.7.2 Patient Selection Criteria . . . . .	90	227
8.3.7.3 Duration of Studies . . . . .	90	227
8.3.7.4 Timing of Visits . . . . .	90	228
8.3.7.5 Number of Patients . . . . .	90	228
8.3.7.6 Choice of Control . . . . .	90	228
8.3.7.7 Selection of Major Clinical Efficacy Endpoints. . . . .	90	228
Objective Tests. . . . .	90	229
Subjective Tests . . . . .	90	231
Tertiary Tests . . . . .	90	232
Pharmacokinetics, Laboratory, and Safety Tests. . . . .	90	233
8.3.8 DRUG CLASS AND GENERAL CONSIDERATIONS. ....	90	234
8.3.9 FDA/SPONSOR DISCUSSIONS . . . . .	90	234
8.3.10 SELECTION OF SPECIAL INTEREST AREAS. ....	90	235
8.3.11 CONCLUSIONS . . . . .	90	235
8.3.12 REFERENCES . . . . .	90	236
8.3.12.1 Study Report References. . . . .	90	236

8.3.12.2 Literature References .....	90	238
<b>8.4 CLINICAL PHARMACOLOGY</b> .....	<b>90</b>	<b>244</b>
8.4.1 INTRODUCTION .....	90	244
8.4.2 ASSESSMENT OF IMMUNE ACTIVATION AND INFLAMMATORY RESPONSE .....	90	244
8.4.3 OCULAR SURFACE INFLAMMATION .....	90	245
8.4.4 PHARMACOLOGIC ACTIVITY .....	90	246
8.4.4.1 Immunomodulation .....	90	247
8.4.4.2 Anti—Inflammatory Activity .....	90	247
8.4.4.3 Modulation of Pathological Apoptosis .....	90	248
8.4.5 CONCLUSIONS .....	90	248
8.4.6 REFERENCES .....	90	248
<b>8.5 LISTING OF INDIVIDUAL STUDY SYNOPSES</b> .....	<b>90</b>	<b>251</b>
8.5.1 OVERVIEW .....	90	251
8.5.2 PHASE 2 CLINICAL STUDY .....	90	252
Table 8.5.2 Phase 2 Clinical Study 192371-001 .....	90	252
8.5.3 PHASE 3 CLINICAL STUDIES .....	90	253
Table 8.5.3-1 Phase 3 Clinical Study 192371-002 .....	90	253
Table 8.5.3-2 Phase 3 Clinical Study 192371-003 .....	90	254
<b>8.6 INTEGRATED SUMMARY OF EFFICACY</b> .....	<b>90</b>	<b>255</b>
8.6.1 INTRODUCTION .....	90	255
8.6.2 ROLE OF THE PHASE 2 STUDY IN DETERMINING PHASE 3 STUDY DESIGN .....	90	255
8.6.3 PHASE 3 STUDY DESIGN AND PATIENT POPULATION .....	90	257
8.6.4 INTENT-TO-TREAT ANALYSIS OF EFFICACY RESULTS .....	90	258
8.6.4.1 Objective Efficacy Measures .....	90	258
Corneal Staining .....	90	258
Schirmer Tear Test with Anesthesia .....	90	260
8.6.4.2 Subjective Efficacy Measures .....	90	261
Blurred Vision .....	90	261
REFRESH Use .....	90	262
8.6.4.3 Responder Analysis .....	90	263
Table 8.6.4.3 Number and Percent of Responders in Phase 3 Studies (Intent-to-Treat Population) .....	90	264
8.6.5 META-ANALYSIS .....	90	264

Table 8.6.5 Statistically Significant Among-Group Differences in the Meta-Analysis of Phase 3 Studies (Intent-to-Treat Population) . . . . .	90	265
<b>8.6.6 SUBGROUP ANALYSES . . . . .</b>	<b>90</b>	<b>265</b>
8.6.6.1 Patients with Severe Disease . . . . .	90	266
Table 8.6.6.1 Statistically Significant Among-Group Differences in the Severe Subgroup of the Phase 3 Studies . . .	90	267
8.6.6.2 Per-Protocol Analysis . . . . .	90	267
Table 8.6.6.2 Statistically Significant Among-Group Differences in Per-Protocol Analysis of the Phase 3 Studies . .	90	268
8.6.6.3 Sjögren’s Syndrome . . . . .	90	269
Table 8.6.6.3 Statistically Significant Among-Group Differences in Patients with Sjögren’s Syndrome in the Phase 3 Studies . . . . .	90	270
8.6.6.4 Other Subgroups . . . . .	90	270
<b>8.6.7 TERTIARY OPHTHALMIC TESTS: EFFECTS OF CYCLOSPORINE EMULSION ON INFLAMMATORY AND IMMUNE MECHANISMS UNDERLYING KCS . . . . .</b>	<b>90</b>	<b>271</b>
8.6.7.1 Baseline Data for Inflammation, Immune Reactivity, and Apoptosis in KCS Patients. . . . .	90	271
Inflammation . . . . .	90	271
Immune Reactivity. . . . .	90	272
Pathological Apoptosis. . . . .	90	272
8.6.7.2 Markers of Inflammation and Immune Reactivity and Goblet Cell Density after 6 Months of Treatment with 0.05% Cyclosporine Ophthalmic Emulsion . . . . .	90	273
Inflammatory Cytokine IL—6 Levels . . . . .	90	273
Lymphocytic and Immune Activation Markers from Conjunctival Biopsies. . . . .	90	274
Goblet Cell Density from Conjunctival Biopsies. . . . .	90	276
<b>8.6.8 PREVIOUS CLINICAL STUDIES SUPPORTING THE EVALUATION OF TOPICAL OPHTHALMIC CYCLOSPORINE FOR THE TREATMENT OF KERATOCONJUNCTIVITIS SICCA. . . . .</b>	<b>90</b>	<b>277</b>
<b>8.6.9 EVIDENCE OF LONG—TERM EFFECTIVENESS, TOLERANCE, AND WITHDRAWAL EFFECTS. . . . .</b>	<b>90</b>	<b>277</b>
<b>8.6.10 DOSE AND REGIMEN RATIONALE. . . . .</b>	<b>90</b>	<b>278</b>
<b>8.6.11 DISCUSSION AND CONCLUSIONS . . . . .</b>	<b>90</b>	<b>278</b>
8.6.11.1 Discussion. . . . .	90	278
8.6.11.2 Conclusions. . . . .	90	281
<b>8.6.12 REFERENCES . . . . .</b>	<b>90</b>	<b>283</b>



8.6.12.1 Study Report References . . . . .	90	283
8.6.12.2 Literature References . . . . .	90	285
<b>8.6.13 TABLES OF PHASE 3 STUDIES POOLED (META-ANALYSIS) . . . . .</b>	<b>90</b>	<b>287</b>
Tables of Phase 3 Studies Pooled . . . . .	90	289
<b>8.6.14 FIGURES . . . . .</b>	<b>90</b>	<b>340</b>
Figure 1 Study 002, ITT: Corneal Staining, Change from Baseline . . . . .	90	341
Figure 2 Study 002, ITT: Schirmer Values (with Anesthesia), Change from Baseline . . . . .	90	342
Figure 3 Study 002, ITT: Blurred Vision Severity, Change from Baseline . . . . .	90	343
Figure 4 Study 002, ITT: Average Daily REFRESH Use During the Previous Week, Change from Baseline . . . . .	90	344
Figure 5 Study 003, ITT: Corneal Staining, Change from Baseline . . . . .	90	345
Figure 6 Study 003, ITT: Schirmer Values (with Anesthesia), Change from Baseline . . . . .	90	346
Figure 7 Study 003, ITT: Blurred Vision Severity, Change from Baseline . . . . .	90	347
Figure 8 Study 003, ITT: Average Daily REFRESH Use During the Previous Week, Change from Baseline . . . . .	90	348
Figure 9 Meta-Analysis: Corneal Staining, Change from Baseline	90	349
Figure 10 Meta-Analysis: Schirmer Values (with Anesthesia), Change from Baseline . . . . .	90	350
Figure 11 Meta-Analysis: Blurred Vision Severity, Change from Baseline . . . . .	90	351
Figure 12 Meta-Analysis: Average Daily REFRESH Use During the Previous Week, Change from Baseline . . . . .	90	352
Figure 13 Study 002, Severe Subgroup: Corneal Staining, Change from Baseline . . . . .	90	353
Figure 14 Study 002, Severe Subgroup: Schirmer Values (with Anesthesia), Change from Baseline . . . . .	90	354
Figure 15 Study 002, Severe Subgroup: Blurred Vision Severity, Change from Baseline . . . . .	90	355
Figure 16 Study 002, Severe Subgroup: Average Daily REFRESH Use During the Previous Week, Change from Baseline . . . . .	90	356
Figure 17 Study 003, Severe Subgroup: Corneal Staining, Change from Baseline . . . . .	90	357
Figure 18 Study 003, Severe Subgroup: Schirmer Values (with Anesthesia), Change from Baseline . . . . .	90	358

Figure 19 Study 003, Severe Subgroup: Blurred Vision Severity, Change from Baseline .....	90	359
Figure 20 Study 003, Severe Subgroup: Average Daily REFRESH Use During the Previous Week, Change from Baseline .....	90	360
8.7 INTEGRATED SUMMARY OF SAFETY .....	91	001
8.7.1 INTRODUCTION .....	91	001
8.7.2 TABULAR SUMMARY OF ALL STUDIES .....	91	002
Table 8.7.2—1 Phase 2 Controlled Clinical Trial of Cyclosporine Ophthalmic Emulsion .....	91	003
Table 8.7.2—2 Phase 3 Controlled Studies of Cyclosporine Ophthalmic Emulsion .....	91	004
Table 8.7.2—2 Phase 3 Controlled Studies of Cyclosporine Ophthalmic Emulsion (continued).....	91	005
8.7.3 OVERALL EXTENT OF EXPOSURE .....	91	006
8.7.3.1 Number of Patients Exposed Overall and for Specified Periods of Time .....	91	006
8.7.3.2 Number of Patients Exposed to Various Doses for Defined Periods .....	91	006
8.7.4 DEMOGRAPHIC AND OTHER CHARACTERISTICS OF STUDY POPULATIONS .....	91	007
8.7.5 ADVERSE EXPERIENCES IN PHASE 3 STUDIES.....	91	008
8.7.5.1 Overall Summary of Adverse Events in Phase 3 Studies ..	91	008
8.7.5.2 Background Summarizing Adverse Events with Systemic Cyclosporine .....	91	009
8.7.5.3 All Adverse Events Regardless of Causality in Phase 3 Studies .....	91	010
Table 8.7.5.3—1 Number (%) of Patients in the Phase 3 Studies with Adverse Events by Relationship to Study Medication and Severity .....	91	011
8.7.5.3-2 Number (%) of Patients in the Phase 3 Studies with Adverse Events by Body System .....	91	012
Table 8.7.5.3—3 Number (%) of Patients in the Phase 3 Studies with Adverse Events Reported by 3% of Patients in Either Cyclosporine Group, Regardless of Causality .....	91	013
8.7.5.4 Treatment—Related Adverse Events in Phase 3 Studies ..	91	015
Table 8.7.5.4 Number (%) of Patients in the Phase 3 Studies with Treatment-Related Adverse Events Reported by 3% of Patients in Either Cyclosporine Group .....	91	016
8.7.5.5 Treatment—Unrelated Adverse Events in Phase 3 Studies	91	016

Table 8.7.5.5 Number (%) of Patients in the Phase 3 Studies with Treatment-Unrelated Adverse Events Reported by 3% of Patients in Either Cyclosporine Group . . . . .	91	017
8.7.5.6 Serious Adverse Events in Phase 3 Studies . . . . .	91	017
8.7.5.7 Discontinuations Due to Adverse Events in Phase 3 Studies . . . . .	91	018
8.7.6 OTHER SAFETY VARIABLES IN PHASE 3 STUDIES . . . . .	91	018
8.7.6.1 Visual Acuity in Phase 3 Studies . . . . .	91	018
8.7.6.2 Intraocular Pressure in Phase 3 Studies . . . . .	91	019
8.7.6.3 Biomicroscopy in Phase 3 Studies . . . . .	91	019
8.7.6.4 Pharmacokinetics in Phase 3 Studies . . . . .	91	020
8.7.7 SUMMARY OF RESULTS FROM PHASE 2 STUDY . . . . .	91	021
8.7.7.1 Adverse Events in Phase 2 Study . . . . .	91	021
Table 8.7.7.1—1 Number (%) of Patients in Phase 2 Study with Adverse Events, Regardless of Causality . . . . .	91	022
Table 8.7.7.1—2 Number (%) of Patients in Phase 2 Study with Treatment—Related Adverse Events . . . . .	91	023
8.7.7.2 Formulation Tolerability in Phase 2 Study . . . . .	91	023
8.7.7.3 Serious Adverse Events and Premature Terminations in Phase 2 Study . . . . .	91	023
8.7.7.4 Blood Chemistry and Hematology in Phase 2 Study . . . . .	91	024
Table 8.7.7.4 Isolated Clinical Laboratory Abnormalities in Phase 2 Study . . . . .	91	025
8.7.7.5 Ocular Microbiology in Phase 2 Study . . . . .	91	026
Table 8.7.7.5—1 Number (%) of Patients in Phase 2 Study with Most Frequently Reported Organisms . . . . .	91	026
Table 8.7.7.5—2 Number (%) of Patients in Phase 2 Study with Organisms Isolated . . . . .	91	027
Table 8.7.7.5—3 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora after 12 Weeks of Treatment . . . . .	91	028
Table 8.7.7.5—4 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora 4 Weeks Post-Treatment . . . . .	91	028
8.7.7.6 Other Safety Variables in Phase 2 Study . . . . .	91	028
8.7.7.7 Pharmacokinetics in Phase 2 Study . . . . .	91	029
8.7.8 DRUG-DRUG INTERACTIONS . . . . .	91	030
8.7.9 DRUG-DEMOGRAPHIC AND DRUG-DISEASE INTERACTIONS . . . . .	91	030
8.7.9.1 Adverse Events by Age Group . . . . .	91	030
Table 8.7.9.1-1 Number (%) of Patients by Age Subgroup in the Phase 3 Studies with Adverse Events by Body System . . . . .	91	031

Table 8.7.9.1-2 Number (%) of Patients by Age Subgroup with the Most Frequently Reported Body as a Whole Adverse Events in the Phase 3 Studies . . . . .	91	032
8.7.9.2 Adverse Events by Sex . . . . .	91	032
Table 8.7.9.2-1 Number (%) of Males and Females in the Phase 3 Studies with Adverse Events by Body System . . . . .	91	033
Table 8.7.9.2-2 Number (%) of Males and Females in the Phase 3 Studies with Adverse Events Overall, in Body as a Whole, and in Skin by Treatment Group . . . . .	91	034
8.7.9.3 Adverse Events by Race . . . . .	91	034
Table 8.7.9.3 Number (%) of Caucasian/Hispanic and Non—Caucasian Patients in the Phase 3 Studies with Adverse Events by Body System . . . . .	91	035
8.7.9.4 Adverse Events by Diagnosis . . . . .	91	036
Table 8.7.9.4 Number (%) of Sjögren’s Syndrome and Non—Sjögren’s Patients in the Phase 3 Studies with Adverse Events by Body System . . . . .	91	037
8.7.9.5 Adverse Events by Iris Color . . . . .	91	038
Table 8.7.9.5 Number (%) of Patients with Dark Irides and Light Irides in the Phase 3 Studies with Adverse Events by Body System . . . . .	91	038
8.7.10 LONG-TERM ADVERSE EFFECTS . . . . .	91	038
8.7.11 WITHDRAWAL EFFECTS . . . . .	91	039
8.7.12 PREVIOUS HUMAN USE OF OTHER FORMULATIONS OF TOPICAL OPHTHALMIC CYCLOSPORINE . . . . .	91	039
8.7.12.1 Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Keratoconjunctivitis Sicca . . . . .	91	039
8.7.12.2 Previous Studies of Other Formulations of Topical Ophthalmic Cyclosporine in Other Indications . . . . .	91	041
8.7.13 SUMMARY OF RESULTS FROM IN-HOUSE ANIMAL STUDIES . . . . .	91	042
8.7.13.1 A Three-Month Ocular and Systemic Toxicity Study with a One-Month Recovery Period in New Zealand White Rabbits . . . . .	91	042
8.7.13.2 A Six-Month Ocular and Systemic Toxicity Study with a Two-Month Recovery Period in New Zealand White Rabbits . . . . .	91	042
8.7.13.3 52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period . . . . .	91	043
8.7.13.4 Margin of Safety Based on Systemic Drug Exposure . . . . .	91	044
8.7.14 DISCUSSION AND CONCLUSIONS . . . . .	91	044
8.7.14.1 Ocular Safety . . . . .	91	044
8.7.14.2 Systemic Safety . . . . .	91	045

8.7.14.3 Conclusions. . . . .	91	046
8.7.15 REFERENCES. . . . .	91	048
8.7.15.1 Study Report References. . . . .	91	048
8.7.15.2 Literature References . . . . .	91	051
8.7.16 TABLES OF PHASE 3 STUDIES POOLED . . . . .	91	055
Tables . . . . .	91	057
8.8 OTHER STUDIES AND INFORMATION. . . . .	91	309
8.8.1 OVERVIEW. . . . .	91	309
8.8.2 ONGOING CONTROLLED CLINICAL STUDIES. . . . .	91	310
Table 8.8.2.-1 Controlled Clinical Study NEI 98—EI—0032 . . . . .	91	310
Table 8.8.2-2 Controlled Clinical Study 192371-501. . . . .	91	311
8.8.3 ONGOING OPEN-LABEL CLINICAL STUDIES. . . . .	91	312
Table 8.8.3-1 Controlled Clinical Study 192371-004. . . . .	91	312
Table 8.8.3-2 Open-Label Clinical Study 192371-005. . . . .	91	313
8.9 DRUG ABUSE AND OVERDOSE. . . . .	91	314
8.9.1 TOPICAL AND SYSTEMIC OVERDOSAGE. . . . .	91	314
8.9.2 ANIMAL SAFETY STUDIES. . . . .	91	314
8.9.3 REFERENCES. . . . .	91	315
8.9.3.1 Study Report References. . . . .	91	315
8.9.3.2 Literature References . . . . .	91	315
8.10 INTEGRATED SUMMARY OF BENEFITS AND RISKS OF THE DRUG. . . . .	91	316
8.10.1 BENEFITS . . . . .	91	316
8.10.2 RISKS. . . . .	91	318
8.10.2.1 Ocular Safety . . . . .	91	319
8.10.2.2 Systemic Safety. . . . .	91	319
8.10.3 CONCLUSIONS . . . . .	91	320
Component. . . . .	91	322
8.10.4.1 Study Report References. . . . .	91	322
8.10.4.2 Literature References . . . . .	91	324
8.11 CLINICAL STUDY REPORTS. . . . .	92	001
8.11.1 STUDY REPORT 192371-001 . . . . .	92	002
192731-001 Study Report, continued. . . . .	92	050
ATTACHMENT 9.0. . . . .	92	098
ATTACHMENT 9.1 Tables. . . . .	92	099
ATTACHMENT 9.2 Tear Protein Report . . . . .	92	278

ATTACHMENT 9.3 Pharmacokinetics Report. . . . .	92	281
ATTACHMENT 10.0 APPENDICES . . . . .	92	296
ATTACHMENT 10.1 Protocol and Amendments. . . . .	92	297
ATTACHMENT 10.2 Randomization Number by Investigator	93	001
ATTACHMENT 10.3 Investigators' CV and Statement of Investigator Forms (FDA 1572, HPB 3005). . . . .	93	012
ATTACHMENT 10.4 List of All IRBs/ERCs Consulted . . . . .	93	200
ATTACHMENT 10.5 Sample Informed Consent Form . . . . .	93	202
ATTACHMENT 10.6 Sample Case Report Forms . . . . .	93	211
ATTACHMENT 10.7 List of Patients by Test Drug Lot Number . . . . .	93	313
ATTACHMENT 10.8 CRFs of Patients with Serious Adverse Events and Patients Discontinued Due to Adverse Events. . . . .	93	314
ATTACHMENT 10.9 Statistical Appendices . . . . .	94	001
8.11.2 STUDY REPORT 192371-002 . . . . .	96	001
SYNOPSIS . . . . .	96	019
1. STUDY IDENTIFICATION . . . . .	96	026
1.1 INVESTIGATOR IDENTIFICATION AND ENROLLMENT . . . . .	96	026
2. INTRODUCTION . . . . .	96	028
3. OBJECTIVE . . . . .	96	029
3.1 OBJECTIVES . . . . .	96	029
3.2 CLINICAL HYPOTHESIS . . . . .	96	029
4. INVESTIGATIONAL PLAN . . . . .	96	030
4.1 OVERALL STUDY DESIGN. . . . .	96	030
4.2 PROTECTION OF HUMAN SUBJECTS. . . . .	96	031
4.3 SELECTION OF CONTROLS . . . . .	96	032
4.4 PATIENT POPULATION. . . . .	96	032
4.5 STUDY TREATMENTS. . . . .	96	037
4.6 CONCOMITANT MEDICATION . . . . .	96	040
4.7 MEASURES OF COMPLIANCE WITH PROTOCOL . . . . .	96	040
4.8 RESPONSE MEASURES . . . . .	96	041
4.9 APPROPRIATENESS AND CONSISTENCY OF MEASURES . . . . .	96	045
4.10 CRITERIA FOR EFFECTIVENESS. . . . .	96	045
4.11 STUDY PROCEDURES . . . . .	96	046
4.12 QUALITY ASSURANCE. . . . .	96	050

4.13 STATISTICAL PLANNING AND ANALYSIS.....	96	052
5. GENERAL STUDY POPULATION RESULTS.....	96	059
5.1 STUDY DURATION.....	96	059
5.2 PATIENT DISPOSITION.....	96	059
5.3 STUDY POPULATION.....	96	060
5.4 DATA SETS ANALYZED.....	96	063
6. RESULTS OF EFFICACY ANALYSIS.....	96	064
6.1 OVERALL SUMMARY OF EFFICACY.....	96	064
6.2 OBJECTIVE SIGNS.....	96	066
6.3 SUBJECTIVE SYMPTOMS.....	96	070
6.4 RESPONDER ANALYSIS.....	96	074
6.5 OTHER VARIABLES.....	96	074
6.6 DRUG-DRUG INTERACTIONS.....	96	076
6.7 SUBGROUP ANALYSES.....	96	076
7. PHARMACOKINETIC RESULTS.....	96	082
8. RESULTS OF SAFETY ANALYSIS.....	96	083
8.1 OVERALL SUMMARY OF SAFETY.....	96	083
8.2 EXTENT OF EXPOSURE.....	96	084
8.3 ADVERSE EVENTS.....	96	085
8.4 OTHER SAFETY VARIABLES.....	96	091
9. DISCUSSION.....	96	094
10. CONCLUSIONS.....	96	096
11. STUDY REPORT REFERENCES.....	96	098
12. LITERATURE REFERENCES.....	96	099
13. ATTACHMENTS.....	96	104
13.1 LIST OF TABLES.....	96	104
13.2 LIST OF FIGURES.....	97	145
13.3 PATIENT NARRATIVES.....	97	154
14. APPENDICES.....	97	167
14.1 PROTOCOL AND AMENDMENTS.....	97	167
14.2 RANDOMIZATION NUMBER BY INVESTIGATOR..	97	268
14.3 PRINCIPAL INVESTIGATORS' CURRICULA VITAE AND COPIES OF STATEMENT OF INVESTIGATOR FORMS 1572.....	98	001
14.4 LIST OF ALL IRBS CONSULTED.....	98	312
14.5 SAMPLE INFORMED CONSENT FORMS.....	98	313

14.6 SAMPLE CASE REPORT FORMS . . . . .	99	001
14.7 PHARMACOKINETICS REPORT. . . . .	99	203
14.8 LIST OF PATIENTS BY TEST DRUG LOT NUMBER. . . . .	99	218
14.9 CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS . . . . .	99	231
14.10 STATISTICAL APPENDICES. . . . .	99	232
8.11.3 STUDY REPORT 192371-003 . . . . .	102	001
SYNOPSIS . . . . .	102	018
1. STUDY IDENTIFICATION . . . . .	102	023
1.1 INVESTIGATOR IDENTIFICATION AND ENROLLMENT . . . . .	102	023
2. INTRODUCTION . . . . .	102	027
3. OBJECTIVE . . . . .	102	028
3.1 OBJECTIVES . . . . .	102	028
3.2 CLINICAL HYPOTHESIS . . . . .	102	028
4. INVESTIGATIONAL PLAN. . . . .	102	029
4.1 OVERALL STUDY DESIGN. . . . .	102	029
4.2 PROTECTION OF HUMAN SUBJECTS. . . . .	102	030
4.3 SELECTION OF CONTROLS . . . . .	102	031
4.4 PATIENT POPULATION. . . . .	102	031
4.5 STUDY TREATMENTS. . . . .	102	036
4.6 CONCOMITANT MEDICATION . . . . .	102	039
4.7 MEASURES OF COMPLIANCE WITH PROTOCOL . . . . .	102	039
4.8 RESPONSE MEASURES . . . . .	102	040
4.9 APPROPRIATENESS AND CONSISTENCY OF MEASURES . . . . .	102	044
4.10 CRITERIA FOR EFFECTIVENESS. . . . .	102	044
4.11 STUDY PROCEDURES . . . . .	102	044
4.12 QUALITY ASSURANCE. . . . .	102	048
4.13 STATISTICAL PLANNING AND ANALYSIS. . . . .	102	049
5. GENERAL STUDY POPULATION RESULTS. . . . .	102	057
5.1 STUDY DURATION. . . . .	102	057
5.2 PATIENT DISPOSITION . . . . .	102	057
5.3 STUDY POPULATION . . . . .	102	058
5.4 DATA SETS ANALYZED . . . . .	102	060
6. RESULTS OF EFFICACY ANALYSIS . . . . .	102	062



6.1 OVERALL SUMMARY OF EFFICACY.....	102	062
6.2 OBJECTIVE SIGNS .....	102	063
6.3 SUBJECTIVE SYMPTOMS .....	102	066
6.4 RESPONDER ANALYSIS .....	102	068
6.5 OTHER VARIABLES.....	102	068
6.6 DRUG-DRUG INTERACTIONS .....	102	070
6.7 SUBGROUP ANALYSES.....	102	071
7. PHARMACOKINETIC RESULTS .....	102	075
8. RESULTS OF SAFETY ANALYSIS .....	102	075
8.1 OVERALL SUMMARY OF SAFETY.....	102	075
8.2 EXTENT OF EXPOSURE .....	102	077
8.3 ADVERSE EVENTS.....	102	077
8.4 OTHER SAFETY VARIABLES.....	102	086
9. DISCUSSION.....	102	088
10. CONCLUSIONS.....	102	090
11. STUDY REPORT REFERENCES.....	102	092
12. LITERATURE REFERENCES .....	102	093
13. ATTACHMENTS.....	102	098
13.1 LIST OF TABLES.....	102	098
13.2 LIST OF FIGURES .....	103	225
13.3 PATIENT NARRATIVES.....	103	234
14. APPENDICES .....	103	242
14.1 PROTOCOL AND AMENDMENTS .....	103	242
14.2 RANDOMIZATION NUMBER BY INVESTIGATOR..	103	332
14.3 PRINCIPAL INVESTIGATORS' CURRICULA VITAE AND COPIES OF STATEMENT OF INVESTIGATOR FORMS 1572 .....	104	001
14.4 LIST OF ALL IRBS CONSULTED .....	105	138
14.5 SAMPLE INFORMED CONSENT FORMS .....	105	140
14.6 SAMPLE CASE REPORT FORMS .....	105	150
14.7 PHARMACOKINETICS REPORT.....	106	001
14.8 LIST OF PATIENTS BY TEST DRUG LOT NUMBER.	106	002
14.9 CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS .....	106	013
14.10 STATISTICAL APPENDICES.....	106	014

8.11.4 INVESTIGATOR SUMMARY REPORT OF NEI 98-0032 BASELINE CONJUNCTIVAL BIOPSY .....	109	001
Signature .....	109	002
Summary Report .....	109	003
8.11.5 INVESTIGATOR SUMMARY REPORT OF BASELINE FLOW CYTOMETRY .....	109	008
Signature .....	109	009
Summary Report .....	109	010
8.11.6 INVESTIGATOR SUMMARY REPORT OF INFLAMMATORY CYTOKINE INTERLEUKIN-6 .....	109	016
Signature .....	109	017
Summary Report .....	109	018
8.11.7 INVESTIGATOR SUMMARY REPORT OF CONJUNCTIVAL BIOPSY .....	109	029
Signature .....	109	030
Summary Report .....	109	031
Figure 1 .....	109	058
Figure 2 .....	109	059
Figure 3 .....	109	060
Figure 4 .....	109	061
Photographs .....	109	062
8.11.8 INVESTIGATOR SUMMARY REPORT OF CONJUNCTIVAL GOBLET CELL DENSITY .....	109	072
Signature .....	109	073
Summary Report .....	109	074
8.11.9 INVESTIGATOR SUMMARY REPORT OF TEAR OSMOLALITY .....	109	094
Signature .....	109	095
Summary Report .....	109	096
8.11.10 OCULAR SURFACE DISEASE INDEX VALIDATION FINAL REPORT .....	109	109
OSDI Appendix 9.1 Protocol .....	109	152
OSDI Appendix 9.2 Sample Case Report Forms .....	109	187
OSDI Appendix 9.3 References .....	109	213
8.11.11 K-201 STUDY REPORT SYNOPSIS: A single-center, double-masked clinical trial to assess safety, ocular tolerability, and initial efficacy of three doses of Sandimmune® ophthalmic ointment in the treatment of vernal keratoconjunctivitis and keratoconjunctivitis sicca. Sandoz 1994 .....	109	265

8.11.12 K-203 ALLERGAN SUMMARY OF SANDOZ CLINICAL STUDY.....	109	267
8.11.13 K-204 STUDY REPORT SYNOPSIS: A double-masked clinical trial to assess safety and efficacy of Sandimmune® 2% ophthalmic ointment vs. placebo in the prevention of graft rejection in "high risk" corneal transplantation patients. Sandoz 1994 .....	109	297
8.11.14 K-206 ALLERGAN SUMMARY OF SANDOZ CLINICAL STUDY.....	109	302
8.11.15 K-301 STUDY REPORT SYNOPSIS: A randomized double-masked clinical trial to assess the safety and efficacy of Sandimmune® 2% ophthalmic ointment vs. placebo in the prevention of graft rejection in "high risk" corneal transplantation patients. Sandoz 1994.....	109	321
8.11.16 PK-95-010 Ocular Pharmacokinetics of Cyclosporine after a Single Eyedrop Instillation of a 0.2% 3H-Cyclosporine Ophthalmic Emulsion into Albino Rabbit Eyes.....	109	334
8.11.17 PK-96-018 Pharmacokinetic Analysis of Cyclosporin A in Human Blood for Clinical Study Entitled "A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05, 0.1, 0.2, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca" .....	109	366
8.11.18 PK-98-109 Six Month Interim Pharmacokinetic Analysis of Trough Blood Concentrations for Study 192371-002 Titled, "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" .....	109	380
8.11.19 PK-98-112 Interim Report of Blood Cyclosporin A Concentrations During One Dosing Interval for Study 192371-002 Titled, "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".....	109	394
8.12 CLINICAL LITERATURE .....	110	001
Adamson 1983.....	110	001
Aragona 1987.....	110	007
Baudouin 1992.....	110	015
Baudouin 1997.....	110	020
Belin 1989.....	110	027
Belin 1990.....	110	034
BenEzra 1988.....	110	046
Berry 1990.....	110	052

Bjerrum 1997.....	110	056
Bleik 1991.....	110	062
Borel 1996.....	110	068
Borel 1996 part b.....	110	131
Boss 1998.....	110	200
Brignole 1998.....	110	209
Castillo 1994.....	110	220
Chen 1990.....	110	221
Colton 1974.....	110	227
Conover 1980.....	110	229
Damato 1984.....	110	250
Drosos 1986.....	110	257
Dustin 1988.....	110	261
Farris 1983.....	110	272
Florio 1996.....	110	278
Foulks 1996.....	110	288
Fox 1986.....	110	289
Fujihara 1997.....	110	296
Gao 1998.....	110	303
Ghalie 1990.....	110	313
Gilbard 1978.....	110	316
Gilbard 1986.....	110	321
Gilbard 1994.....	110	334
Gipson 1997.....	110	344
Goichot 1988.....	110	362
Griffiths 1990.....	111	001
Gunduz 1993.....	111	007
Gunduz 1994.....	111	012
Gunduz 1997.....	111	017
Helms 1996.....	111	021
Hess 1993.....	111	022
Hikichi 1995.....	111	031
Hodgkin 1987.....	111	035
Hoffmann 1985.....	111	043
Hoffmann 1985/1986.....	111	048
Holland 1993.....	111	053

Holly 1977	111	060
Iacono 1997	111	079
Ippolito 1993	111	088
Jabs 1988	111	099
Janeway 1994	111	106
Jones 1994	111	115
Kahan 1983	111	127
Kahan 1989	111	137
Kahan 1994	111	151
Kaswan 1989	111	163
Kaswan 1990	111	170
Kaswan 1994	111	201
Kervick 1992	111	213
Kronbach 1988	111	222
Laibovitz 1993	111	228
Lemp 1995	111	237
Lemp 1997	111	249
Lubniewski 1990	111	262
Mackie 1984	111	282
Mantel 1980	111	286
Matsue 1995	111	305
Matsumoto 1996	111	311
McCarty 1998	111	320
Memon 1995	111	326
Meyer 1997	111	330
Mircheff 1994	111	335
Mitruka 1998	111	344
Morgan 1991	111	354
Mosmann 1989	112	001
Norn 1973	112	030
Nussbaum 1995	112	039
Olivero 1991	112	042
Oran 1997	112	046
Ormerod 1988	112	054
Oyer 1983	112	061
Palmer 1996	112	068

Patel 1989 .....	112	072
Pathak 1980 .....	112	076
PDR-METHOTREXATE 1998.....	112	084
PDR-NEORAL 1998.....	112	103
PDR-SANDIMMUNE 1998 .....	112	132
Pepose 1990.....	112	146
Pette 1997 .....	112	153
Pflugfelder 1986 .....	112	162
Pflugfelder 1990 .....	112	167
Pflugfelder 1996 .....	112	174
Pflugfelder 1997 .....	112	175
Pflugfelder 1999 .....	112	188
Philip 1994.....	112	220
Power 1993 .....	112	224
Ralph 1975.....	112	229
Raphael 1988.....	112	233
Ren 1996 .....	112	245
Romagnani 1991 .....	112	254
Salisbury 1995.....	112	256
Sanders 1986 .....	112	261
SAS 1996.....	112	301
Sayama 1994 .....	112	306
Schein 1997 .....	112	311
Schliephake 1997.....	112	317
Scorrano 1997 .....	112	321
Seal 1985.....	112	325
Secchi 1990 .....	112	333
Secchi 1997 .....	112	338
Smith 1999.....	112	340
Solch 1991 .....	112	341
Starzl 1983a.....	112	352
Starzl 1983b.....	113	001
Stern 1998 .....	113	005
Sullivan 1994.....	113	011
Sumida 1995 .....	113	019
Svecova 1998.....	113	025

Takaya 1997.....	113	031
Tornheim 1980.....	113	036
Tseng 1985.....	113	037
Tsubota 1991.....	113	043
van der Pouw Kraan 1996.....	113	046
Vitali 1993.....	113	052
Wakefield 1992.....	113	060
White 1993.....	113	065
Wiebking 1986.....	113	072
Williamson 1973.....	113	075
Wilson 1996a.....	113	082
Wilson 1996b.....	113	093
Zhao 1993.....	113	106
Zhao 1995.....	113	114
Zierhut 1989.....	113	120
<b>Section 11 CASE REPORT TABULATIONS.....</b>	<b>114</b>	<b>006</b>
STUDY REPORT 192731-001.....	114	006
192731-001 CASE REPORT TABULATIONS.....	114	007
Listing 1 Patient Screening Qualifications.....	114	008
Listing 2 Demographics.....	114	018
Listing 3 Medical History.....	114	023
Listing 4 Ophthalmic History.....	114	040
Listing 5 Pregnancy Test.....	114	045
Listing 6 Dry Eye History.....	114	050
Listing 7 Dry Eye History: Artificial Tear Products Used.....	114	056
Listing 8 Other Artificial Tear Products Currently Used.....	114	082
Listing 9 Other Artificial Tear Products Used in the Past.....	114	087
Listing 10 Dry Eye History: Tear Regimen.....	114	092
Listing 11 Dry Eye History: Eye Symptoms.....	114	098
Listing 11 Dry Eye History: Eye Symptoms, continued.....	114	103
Listing 12 Dry Eye History: Eye Symptoms Diagnosis.....	114	136
Listing 13 Dry Eye History: Alcohol.....	114	153
Listing 14 Dry Eye History: Other Questions.....	114	158
Listing 15 Disease History: Disease Diagnosis.....	114	164
Listing 16 Disease History.....	114	174
Listing 17 Sjogren's Syndrome Disease History: Xerostomia.....	114	179

Listing 18 Sjogren's Lip Biopsy, Associated Diseases. . . . .	114	184
Listing 19 Sjogren's Salivary Gland. . . . .	114	189
Listing 20 Symptoms of Ocular Discomfort . . . . .	114	194
Listing 20 Symptoms of Ocular Discomfort, continued (a) . . . . .	114	198
Listing 20 Symptoms of Ocular Discomfort, continued (b) . . . . .	114	293
Listing 20 Symptoms of Ocular Discomfort, continued (c) . . . . .	115	001
Listing 20 Symptoms of Ocular Discomfort, continued (d) . . . . .	115	096
Listing 20 Symptoms of Ocular Discomfort, continued (e) . . . . .	115	191
Listing 20 Symptoms of Ocular Discomfort, continued (f). . . . .	115	286
Listing 20 Symptoms of Ocular Discomfort, continued (g) . . . . .	116	001
Listing 21 Visual Acuity. . . . .	116	066
Listing 21 Visual Acuity, continued . . . . .	116	096
Listing 22 Biomicroscopy, Part 1. . . . .	116	106
Listing 22 Biomicroscopy, Part 1, continued (a) . . . . .	116	201
Listing 22 Biomicroscopy, Part 1, continued (b) . . . . .	116	296
Listing 22 Biomicroscopy, Part 1, continued (c) . . . . .	117	001
Listing 23 Biomicroscopy Part 2 . . . . .	117	036
Listing 23 Biomicroscopy Part 2, continued . . . . .	117	096
Listing 24 Superficial Punctate Keratitis . . . . .	117	102
Listing 24 Superficial Punctate Keratitis, continued. . . . .	117	191
Listing 25 Schirmer's II Test . . . . .	117	286
Listing 26 Vital Signs. . . . .	117	329
Listing 27 Drug Instillation Times . . . . .	117	344
Listing 27 Drug Instillation Times, continued . . . . .	118	001
Listing 28 Test Samples Collected . . . . .	118	015
Listing 28 Test Samples Collected, continued . . . . .	118	096
Listing 29 Tear Break-up Time . . . . .	118	118
Listing 30 Rose Bengal Staining . . . . .	118	190
Listing 30 Rose Bengal Staining, continued. . . . .	118	288
Listing 31 IOP . . . . .	118	343
Listing 32 Formulation Tolerability . . . . .	118	368
Listing 32 Formulation Tolerability, continued (a) . . . . .	119	001
Listing 32 Formulation Tolerability, continued (b) . . . . .	119	096
Listing 33 Patient Status: Washout Phase . . . . .	119	144
Listing 34 OSD Quality of Life Questionnaire . . . . .	119	150
Listing 34 OSD Quality of Life Questionnaire, continued (a) . . . . .	119	192



Listing 34 OSD Quality of Life Questionnaire, continued (b) . . . . .	119	287
Listing 35 Global Evaluation of Response to Treatment . . . . .	119	335
Listing 36 Formulation Tolerability: Follow-up Visits . . . . .	119	369
Listing 36 Formulation Tolerability: Follow-up Visits, continued . . .	120	001
Listing 37 Additional Blood Draws for Cyclosporin-A Concentrations .	120	099
Listing 38 Adverse Events - Part 1 . . . . .	120	104
Listing 39 Adverse Events - Outcome - Part 2 . . . . .	120	112
Listing 40 Subject Perspective - Would Buy Drug . . . . .	120	118
Listing 41 Subject Perspective - Would Not Buy Drug . . . . .	120	124
Listing 42 Diary Part A - Symptoms . . . . .	120	129
Listing 42 Diary Part A - Symptoms, continued (a) . . . . .	120	194
Listing 42 Diary Part A - Symptoms, continued (b) . . . . .	120	289
Listing 42 Diary Part A - Symptoms, continued (c) . . . . .	121	001
Listing 42 Diary Part A - Symptoms, continued (d) . . . . .	121	096
Listing 42 Diary Part A - Symptoms, continued (e) . . . . .	121	191
Listing 43 Diary Part B - Refresh Use . . . . .	121	221
Listing 43 Diary Part B - Refresh Use, continued . . . . .	121	286
Listing 44 Face (Facial Expression) . . . . .	121	301
Listing 45 Concomitant Medications . . . . .	122	001
Listing 46 Serious Adverse Event Concomitant Medications . . . . .	122	019
Listing 47 Lab Analysis . . . . .	122	020
Listing 47 Lab Analysis, continued (a) . . . . .	122	114
Listing 47 Lab Analysis, continued (b) . . . . .	122	209
Listing 47 Lab Analysis, continued (c) . . . . .	122	304
Listing 47 Lab Analysis, continued (d) . . . . .	123	001
Listing 47 Lab Analysis, continued (e) . . . . .	123	096
Listing 48 Microbiology . . . . .	123	156
Listing 49 Lab Sjogren's Test . . . . .	123	170
Listing 50 Brush Cytology . . . . .	123	184
Listing 50 Brush Cytology, continued . . . . .	123	191
Listing 51 Patient Exit Status . . . . .	123	203
STUDY REPORT 192731-002 . . . . .	124	001
192731-002 CASE REPORT TABULATIONS . . . . .	124	002
Listing 1 Screening Criteria . . . . .	124	003
Listing 2 Date of Informed Consent . . . . .	124	057
Listing 3 Inclusion/Exclusion . . . . .	124	099

Listing 4 Patient History and Demographics . . . . .	124	144
Listing 5 Medical History . . . . .	125	001
Listing 6 Ophthalmic History . . . . .	125	141
Listing 7 Dry Eye History . . . . .	125	261
Listing 8 Related Systematic Dry Eye History . . . . .	125	303
Listing 9 Associated Diseases . . . . .	125	345
Listing 10 Symptoms of Discomfort (from dry eye) . . . . .	126	001
Listing 10 Symptoms of Discomfort, continued . . . . .	127	001
Listing 11 Facial Expression Subjective Rating Scale . . . . .	127	130
Listing 12 Ocular Surface Disease Index . . . . .	128	001
Listing 12 Ocular Surface Disease Index, continued . . . . .	129	001
Listing 13 Corneal and Interpalpebral Staining . . . . .	130	001
Listing 14 Schirmer Test . . . . .	130	084
Listing 15 Biomicroscopy Meibomian Glands . . . . .	130	195
Listing 16 Biomicroscopy . . . . .	131	001
Listing 16 Biomicroscopy, continued . . . . .	132	001
Listing 17 Cyclosporine Use . . . . .	132	164
Listing 18 Use of Refresh (R) . . . . .	132	206
Listing 19 ETDRS Visual Acuity . . . . .	132	281
Listing 20 Tear Osmolality . . . . .	132	420
Listing 21 Tear Break-Up Time . . . . .	133	001
Listing 22 Study Eye for Tertiary Tests . . . . .	133	239
Listing 23 Intraocular Pressure . . . . .	133	281
Listing 24 Masked Medication Use Prior to Visit . . . . .	133	326
Listing 25 Month 4 Use of Refresh (R) . . . . .	134	001
Listing 26 Global Response to Treatment . . . . .	134	038
Listing 27 Sjogrens Syndrome Serum Antibodies . . . . .	134	093
Listing 28 Sjogrens Syndrome Serum Antibodies Lab Values . . . . .	134	120
Listing 29 Prior Medications . . . . .	135	001
Listing 30 Concomitant Medications . . . . .	136	001
Listing 31 Concurrent Procedures . . . . .	136	139
Listing 32 Examination Dates and Times . . . . .	136	166
Listing 33 Adverse Events . . . . .	136	255
Listing 34 Serious Adverse Events . . . . .	137	001
Listing 35 Adverse Events Comments . . . . .	137	011
Listing 36 General Comments . . . . .	137	039

Listing 37 Subject Status at Day 0 . . . . .	137	050
Listing 38 Patient Disposition . . . . .	137	092
STUDY REPORT 192731-003 . . . . .	138	001
192731-003 CASE REPORT TABULATIONS . . . . .	138	002
Listing 1 Screening Criteria . . . . .	138	003
Listing 2 Date of Informed Consent . . . . .	138	083
Listing 3 Inclusion/Exclusion . . . . .	138	152
Listing 4 Patient History and Demographics . . . . .	138	221
Listing 5 Medical History . . . . .	139	001
Listing 6 Ophthalmic History . . . . .	139	117
Listing 7 Dry Eye History . . . . .	139	195
Listing 8 Related Systematic Dry Eye History . . . . .	139	264
Listing 9 Associated Diseases . . . . .	139	333
Listing 10 Symptoms of Discomfort (from dry eye) . . . . .	140	001
Listing 10 Symptoms of Discomfort, continued . . . . .	141	001
Listing 11 Facial Expression Subjective Rating Scale . . . . .	141	296
Listing 12 Ocular Surface Disease Index . . . . .	142	001
Listing 12 Ocular Surface Disease Index, continued . . . . .	143	001
Listing 12 Ocular Surface Disease Index, continued . . . . .	144	001
Listing 13 Corneal and Interpalpebral Staining . . . . .	144	140
Listing 14 Schirmer Test . . . . .	144	255
Listing 15 Biomicroscopy Meibomian Glands . . . . .	145	001
Listing 16 Biomicroscopy . . . . .	145	102
Listing 16 Biomicroscopy, continued . . . . .	146	001
Listing 17 Cyclosporine Use . . . . .	146	182
Listing 18 Use of Refresh (R) . . . . .	146	251
Listing 19 ETDRS Visual Acuity . . . . .	147	001
Listing 20 Tear Osmolality . . . . .	147	172
Listing 21 Tear Break-Up Time . . . . .	147	183
Listing 22 Study Eye for Tertiary Tests . . . . .	148	001
Listing 23 Intraocular Pressure . . . . .	148	070
Listing 24 Masked Medication Use Prior to Visit . . . . .	148	139
Listing 25 Month 4 Use of Refresh (R) . . . . .	148	223
Listing 26 Global Response to Treatment . . . . .	148	283
Listing 27 Sjogrens Syndrome Serum Antibodies . . . . .	148	363
Listing 28 Sjogrens Syndrome Serum Antibodies Lab Values . . . . .	149	001

Listing 29 Prior Medications . . . . .	149	193
Listing 30 Concomitant Medications . . . . .	150	001
Listing 31 Concurrent Procedures . . . . .	150	199
Listing 32 Examination Dates and Times. . . . .	150	238
Listing 33 Adverse Events . . . . .	151	001
Listing 34 Serious Adverse Events. . . . .	151	201
Listing 35 Adverse Event Comments. . . . .	151	217
Listing 36 General Comments . . . . .	151	249
Listing 37 Subject Status at Day 0 . . . . .	151	261
Listing 38 Patient Disposition . . . . .	151	330
<b>Section 12 CASE REPORT FORMS . . . . .</b>	<b>152</b>	<b>003</b>
STUDY REPORT 192731-001 . . . . .	152	003
192731-001 CASE REPORT FORMS . . . . .	152	004
CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS . . . . .	152	005
CRFs for Patients with Serious Adverse Events . . . . .	152	006
CRFS OF PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS . . . . .	152	014
CRFs for Discontinued Patients. . . . .	152	015
STUDY REPORT 192731-002. . . . .	152	020
192731-002 CASE REPORT FORMS . . . . .	152	021
CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS . . . . .	152	021
Berdy, Investigator 2697 . . . . .	152	022
SUBJECT 228. . . . .	152	022
SUBJECT 412. . . . .	152	113
Epstein, Investigator 2702 . . . . .	152	185
SUBJECT 278. . . . .	152	185
Foerster, Investigator 0207 . . . . .	152	239
SUBJECT 198. . . . .	152	239
SUBJECT 201. . . . .	152	329
SUBJECT 315. . . . .	153	001
SUBJECT 319. . . . .	153	077
SUBJECT 323. . . . .	153	153
SUBJECT 489. . . . .	153	247
Forstot, Investigator 0595 . . . . .	154	001
SUBJECT 104. . . . .	154	001

Heidemann, Investigator 2705. ....	154	065
SUBJECT 162. ....	154	065
Nelson, Investigator 0768 . ....	154	138
SUBJECT 270. ....	154	138
SUBJECT 271. ....	154	234
SUBJECT 274. ....	154	309
O'Day, Investigator 2706. ....	155	001
SUBJECT 171. ....	155	001
SUBJECT 178. ....	155	086
SUBJECT 329. ....	155	177
SUBJECT 336. ....	155	257
SUBJECT 337. ....	155	347
SUBJECT 338. ....	156	001
SUBJECT 497. ....	156	091
SUBJECT 499. ....	156	155
Perry, Investigator 1777. ....	156	247
SUBJECT 180. ....	156	247
SUBJECT 193. ....	156	338
Sall, Investigator 2707. ....	157	001
SUBJECT 110. ....	157	001
SUBJECT 115. ....	157	046
SUBJECT 128. ....	157	100
SUBJECT 129. ....	157	193
SUBJECT 292. ....	157	251
SUBJECT 346. ....	157	312
SUBJECT 435. ....	157	357
SUBJECT 471. ....	158	001
SUBJECT 512. ....	158	092
SUBJECT 513 (1 OF 2) . ....	158	186
SUBJECT 513 (2 OF 2) . ....	158	247
Schiffman, Investigator 2430. ....	158	286
SUBJECT 262. ....	158	286
SUBJECT 265. ....	158	340
Stevenson, Investigator 2366. ....	159	001
SUBJECT 386. ....	159	001
SUBJECT 387. ....	159	092

SUBJECT 388.....	159	186
SUBJECT 399.....	159	254
SUBJECT 449.....	159	349
SUBJECT 450.....	160	001
SUBJECT 457.....	160	051
SUBJECT 479.....	160	145
SUBJECT 480.....	160	235
Stewart, Investigator 1783.....	160	299
SUBJECT 302.....	160	299
SUBJECT 312.....	161	001
SUBJECT 402.....	161	074
SUBJECT 406.....	161	163
Trocme, Investigator 2709.....	161	212
SUBJECT 233.....	161	212
SUBJECT 234.....	162	001
SUBJECT 236 (1 OF 2).....	162	094
SUBJECT 236 (2 OF 2).....	162	168
SUBJECT 237.....	162	242
SUBJECT 250.....	162	334
STUDY REPORT 192731-003.....	163	001
192731-003 CASE REPORT FORMS.....	163	002
CRFS OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND PATIENTS DISCONTINUED DUE TO ADVERSE EVENTS.....	163	002
Barber, Investigator 2696.....	163	003
SUBJECT 293.....	163	003
SUBJECT 404.....	163	081
SUBJECT 406 (1 OF 2).....	163	135
SUBJECT 406 (2 OF 2).....	163	215
SUBJECT 417 (1 OF 2).....	163	240
SUBJECT 417 (2 OF 2).....	163	320
SUBJECT 420.....	164	001
SUBJECT 466.....	164	092
Burke, Investigator 2798.....	164	181
SUBJECT 572.....	164	181
SUBJECT 599.....	164	243
Cavanaugh, Investigator 0416.....	165	001

SUBJECT 489.....	165	001
Donshik, Investigator 0200 .....	165	061
SUBJECT 225.....	165	061
SUBJECT 228.....	165	113
Friedlaender, Investigator 0286.....	165	200
SUBJECT 505.....	165	200
Gruber, Investigator 2704 .....	166	001
SUBJECT 102.....	166	001
SUBJECT 104.....	166	063
SUBJECT 105.....	166	161
SUBJECT 109 (1 OF 2) .....	166	251
SUBJECT 109 (2 OF 2) .....	166	331
SUBJECT 389.....	166	358
Laibovitz, Investigator 1438 .....	167	001
SUBJECT 528 .....	167	001
SUBJECT 563.....	167	052
SUBJECT 565.....	167	113
SUBJECT 593.....	167	203
McGarey, Investigator 2821 .....	168	001
SUBJECT 538.....	168	001
Mundorf, Investigator 1485.....	168	089
SUBJECT 263 (1 OF 2) .....	168	089
SUBJECT 263 (2 OF 2) .....	168	169
SUBJECT 585 (1 OF 2) .....	168	194
SUBJECT 585 (2 OF 2) .....	168	275
Ostrov, Investigator 1796 .....	169	001
SUBJECT 131.....	169	001
SUBJECT 242.....	169	092
Pflugfelder, Investigator 1272.....	169	182
SUBJECT 274.....	169	182
SUBJECT 287.....	169	231
Sansone, Investigator 2794 .....	169	280
SUBJECT 332.....	169	280
SUBJECT 520.....	169	317
SUBJECT 602.....	169	365
Schanzlin, Investigator 0369 .....	170	001

SUBJECT 194.....	170	001
SUBJECT 195.....	170	049
Stamler, Investigator 1838.....	170	133
SUBJECT 126.....	170	133
SUBJECT 127.....	170	185
SUBJECT 322.....	170	247
SUBJECT 325.....	170	251
Williams, Investigator 2710.....	170	343
SUBJECT 578.....	170	344
Yee, Investigator 2298.....	171	001
SUBJECT 207.....	171	002



**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.

<u>Submission Date</u>	<u>IND Serial Number</u>	<u>Subject/Interaction</u>
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.

Dr. Chambers  
Letter of Understanding, IND 32,133  
Page 2 of 2  
August 26, 1996

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  
Director  
Regulatory Affairs



## ALLERGAN

3525 DuPont Drive, P.O. Box 1534, Irvine, CA 92620-9534 (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.

E. Bancroft Regulatory Affairs  
B. Reis Clinical Research  
K. Stern Biostatistics

FDA

J. Bull Medical Officer  
W. Chambers Acting Director, HFD-550  
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

lou2

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 outlined 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 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

lou2



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

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  
Director  
Regulatory Affairs

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

lou2



**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, Manufacturing 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:

<u>Allergan, Inc.</u>		<u>FDA</u>	
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.

lou3

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.

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

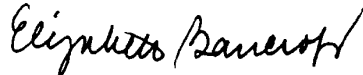
With an appropriate washout period, patients with previous exposure to a topical cyclosporine formulation may be enrolled in the Allergan phase 3 clinical trial. It was clarified subsequent to this meeting, in a telephone call on May 8, 1997 between Dr. Chambers and Elizabeth Bancroft, that these patients 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  
Director  
Regulatory Affairs



**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  
Director  
Regulatory Affairs

cc: B. Reis, Allergan

lou3





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

**FDA TELEPHONE CONTACT**

<b>TO:</b>	LIST	<b>SUBJECT:</b>	Statistical plan for cyclosporine ophthalmic emulsion
<b>FROM:</b>	E. Bancroft <i>EB</i>	<b>DATE:</b>	25 June 1998
<b>COPIES:</b>	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.

Memo, Stat Plan CsA  
June 25, 1998  
Page 2 of 2

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) 248-4500 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

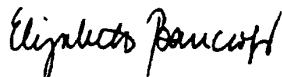
1. Allergan proposed doing a meta-analysis of efficacy across the 2 pivotal clinical studies. The Agency indicated that this type of analysis was not useful. Each study should stand alone and each should meet safety and efficacy criteria.
2. Allergan proposed doing an analysis of efficacy combining both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

Letter of understanding, preNDA meeting  
Cyclosporine ophthalmic emulsion  
December 7, 1998  
Page 2 of 2

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  
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](http://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:

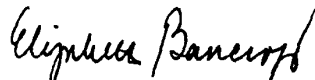
<u>Item Number</u>	<u>Description of Item</u>
Section 4A.3.4.7	Completion of the commercial-scale batch results table
Appendix 4A.5.3.2	Aseptic process validation report

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



**1.3.2.1.1  
REFERENCES**

### 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:

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

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,

A handwritten signature in dark ink, appearing to read "Ronald G. Van Valen".

Ronald G. Van Valen  
Associate Director  
Drug Regulatory Affairs

attachment

cc: L. Zipper

**LIST OF CROSS-REFERENCED INDs and NDAs**

<u>IND No.</u>	<u>DESCRIPTION</u>
32,133	Sandimmune® 2% Ophthalmic Ointment (IND transfer to Allergan Inc.; letter dated September 29, 1994)
16,450	Sandimmune® Oral Solution/Soft Gelatin Capsules (cyclosporine, USP) Indication: Prophylaxis of organ rejection Documentation currently resides within the FDA Division of Special Pathogens and Immunologic Drug Products/HFD-590
<u>NDA No.</u>	<u>DESCRIPTION</u>
50-574	Sandimmune® Oral Solution (cyclosporine oral solution, USP) Indication: Prophylaxis of organ rejection 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) Indication: Prophylaxis of organ rejection 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  
Director  
Regulatory Affairs

EB:mkb







December 16, 1993

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

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

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

**1.4 PATENT  
INFORMATION**

**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*

*Feb 4, 1999*

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.<sup>4</sup>** ..... 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)—Boisjoly 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.  
Boisjoly 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

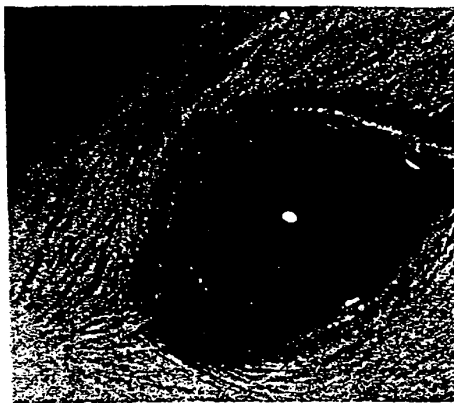
[57] **ABSTRACT**  
The present invention relates to a method for the treatment of either phacoanaphylactic endophthalmitis or uveitis by administering at least one cyclosporin topically to the eyes. Topical application of cyclosporin provides cyclosporin to the anterior chamber, the posterior chamber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

20 Claims, 6 Drawing Figures

U.S. Patent Mar. 10, 1987 Sheet 1 of 3 4,649,047



*FIG. 1a*

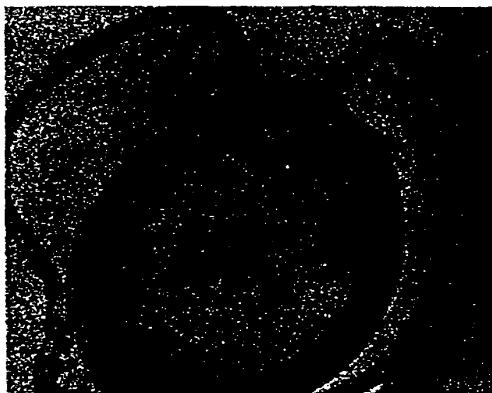


*FIG. 2a*

U.S. Patent Mar. 10, 1987 Sheet 2 of 3 4,649,047



*FIG. 1b*



*FIG. 2b*

U.S. Patent Mar. 10, 1987 Sheet 3 of 3 4,649,047

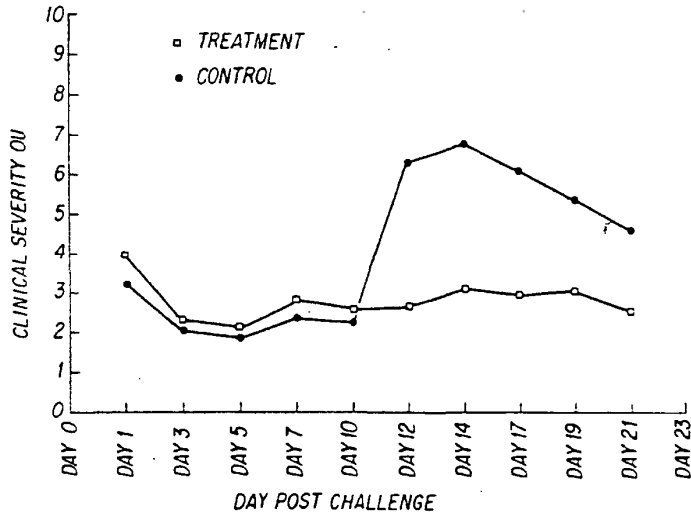


FIG. 3a

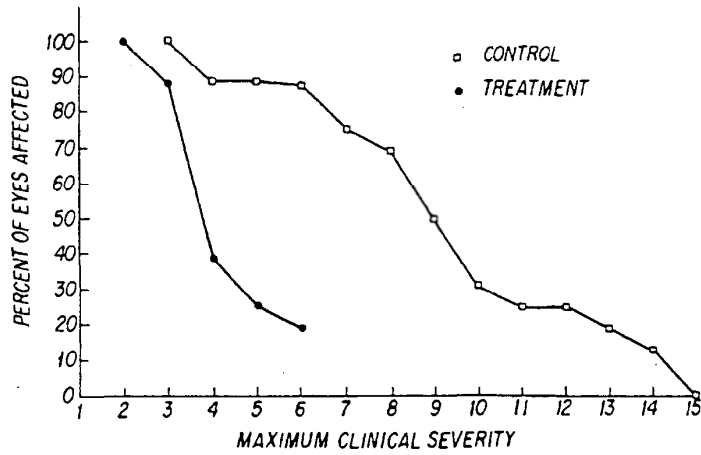


FIG. 3b



4,649,047

1

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 eye. 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 uveitides.

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 causative 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

2

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 cul-de-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. Ophthalmol.* (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., cyclophosphamide, azathioprine 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 ophthalmic 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 endophthalmitis 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 ophthalmic 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 efficacious in the treatment of phacoanaphylactic endophthalmitis or uveitis found

4,649,047

3

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

4

FIG. 1b is a photograph of the microscopic appearance (x23) of phacoanaphylaxis from an untreated control rat eye.

FIG. 2a 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. 2b is a photograph of a microscopic section (x23) of a rat eye 14 days following Cyclosporine topical therapy.

FIG. 3a 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. 3b illustrates the data of FIG. 3a 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 occurring throughout the globe of the eye by topical administration 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 phacoanaphylactic 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 efficacious 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)						# Eyes
	Tissue Cornea	Aqueous	Lens	Anterior Vitreous	Posterior Vitreous	Blood	
Oral 20 mg/kg/day x 4 days	<250	<60	<250	<60	<60	617	12
Ophthalmic 2% oil	6,640 (3,600-11,600)	<60 (ND)	<250	<60	<60	ND	8
Q 15 min x 6 Ophthalmic 2% ointment	9,750 (5,600-14,400)	<60 (20)	<250	325 (80-1,450)	690 (425-800)	ND	6
Q 15 min x 6 Ophthalmic 2% oil	15,140 (7,300-27,500)	<60 (24)	<250	2,400 (500-4,700)	400 (250-525)	ND	8

5

4,649,047

6

TABLE-continued

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

Legend:  
ND = not determined  
QID = 4 times daily  
Q 15 min X 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. 3a and 3b demonstrate the efficacy of topical cyclosporine administration.

The graph of FIG. 3a 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 inflamed 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. 3b illustrates the same data differently. FIG. 3b 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 ob-

served 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 efficacious 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: microdome, 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-

4,649,047

7

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 ophthalmic 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. 1a 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. 1b 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 (1). The globe of the eye is approximately 30% reduced in size due to phthisis.

FIG. 2a 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. 2b 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, *Ophthalm 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 anesthetized with Ketamine HCl 10 mg/kg intramuscularly. With the aid of a dissecting 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 anti-inflammatory 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

8

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 dissecting 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 abscessation, neovascularization and panophthalmitis (FIG. 1a). Four eyes progressed to a phthisis bulbi. Histopathology of these eyes revealed a aseptic granulomatous panophthalmitis. A zonal distribution of neutrophils and macrophages occurred around the ruptured lens capsule where early cataractous changes were evident. A cyclitic membrane formed behind the lenses. The anterior chamber, iris, vitreous humor and retina were densely infiltrated with lymphocytes (FIG. 1b). On histopathologic examination, 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. 2a). At forty-eight hours post operatively, one eye had a small central corneal abscess which resolved by day five. On histopathologic examination, the lens capsules were torn and the subjacent lens cataractous, but little or no inflammation was associated with the injury (FIG. 2b). 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  $\ddagger$  with phacoanaphylaxis,  $\ddagger$  with anterior uveitis and 2/8 not inflamed.

#### 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.

4,649,047

9

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 5 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 digested 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 15 obtained for each compartment.

TABLE

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

\*Iris and ciliary body 749, retina 483.

Legend:

ND = not determined

QID = 4 times daily

Q 15 min x 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 45 oil was applied to the eyes every 15 minutes for 6 appli-

10

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 1st 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 micograms 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.

Clinical observation	Scheme for Grading Uveitis in Animals injected with Human Serum Albumin				
	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	opaque
Vitreous & retina	Chorioretinal detail sharp	Chorioretinal detail visible but blurred	fair red reflex	poor red reflex	no red reflex

Note:

Corneal neovascularization

retinal detachments

hypopyon

hyphema

fibrous deposition

iris bombe, depth of anterior chamber

cations followed by 60 minutes to allow for absorption. 3 rabbits, 6 eyes, were used. The eyes were frozen, 65 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

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

4,649,047

11

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

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.

12

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, polyoxyethylated castor oil or methyl cellulose or a mixture thereof.

12. The method of claim 4 wherein the medically suitable excipient comprises polyvinyl alcohol, polyoxyethylated 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 phacoanaphylactic endophthalmitis.

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 vitreous body of an eye, which comprises topically administering to said eye an amount of a cyclosporin sufficient to reduce said immune activity.

\* \* \* \* \*

55

60

65



**United States Patent** [19]

Kaswan

[45] Date of Patent: \* Jun. 13, 1989

[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.

[21] Appl. No.: 92,466

[22] Filed: Sep. 3, 1987

[51] Int. Cl.<sup>4</sup> ..... A61K 37/02

[52] U.S. Cl. .... 514/11; 514/915

[58] Field of Search ..... 424/78; 514/11, 9, 912, 514/914, 915, 15; 530/317

[56] References Cited

U.S. PATENT DOCUMENTS

4,108,985	8/1978	Ruegger et al.	514/11
4,117,118	9/1978	Harri et al.	514/11
4,210,581	7/1980	Ruegger et al.	530/321
4,215,199	7/1980	Harri et al.	435/71
4,220,641	9/1980	Traber et al.	514/11
4,220,657	9/1980	Johnson et al.	514/912
4,288,431	9/1981	Traber et al.	514/11
4,289,851	9/1981	Traber et al.	435/71
4,384,996	5/1983	Bollinger et al.	530/321
4,388,307	6/1983	Cavanak	514/11
4,396,542	8/1983	Wenger	530/32
4,452,818	6/1984	Haidt	514/912
4,554,351	11/1985	Wenger	514/11
4,639,434	1/1987	Wenger et al.	514/11
4,649,047	3/1987	Kaswan	514/11
4,681,754	7/1987	Siegl	424/10
4,703,033	10/1987	Seebach	514/11

FOREIGN PATENT DOCUMENTS

19197	3/1972	Australia	424/78
8404681	12/1984	PCT Int'l Appl.	514/912
8501875	5/1985	PCT Int'l Appl.	514/914
8603966	7/1986	PCT Int'l Appl.	514/912

OTHER PUBLICATIONS

Kaswan et al., *Am. J. Vet. Res.* 46, 376-383 (1985).  
 Wenger, *Synthesis of Cyclosporin and Analogues*, pp. 14-25 in *Cyclosporin* vol. 1, Grune & Stratton, Inc. (New York, 1983).  
 BenEzra et al., *Amer. J. Ophthalmol.* 101, 278-282 (1986).  
 Hunter et al., *Clin. Exp. Immunol.* 45, 173-177 (1981).  
 Boisjoly et al., *Arch. Ophthalmol.* 102, 1804-1807 (1984).  
 Mosteller et al., *Investigative Ophthalmol. Supp.* 25, 3, 38 (1984).  
 Nussenblatt et al., *Amer. J. Ophthalmol.* 96, 275-282 (1983).  
 Hoffman, et al., *Kin. Mbl. Augenheilk.* 187, 92-95 (1985) and certified translation thereof.  
 "Aspirin Therapy in Vernal Conjunctivitis" by Abelson, et al., *Amer. J. Ophthal.* 95,502-505 (1983).  
 "Cryosurgery in the Management of Vernal Keratoconjunctivitis" by Abiose, et al., *Annals of Ophthal.* 15(8), 744-747 (1983).  
 "Vernal Conjunctivitis" by Allansmith, Chapter 9, pp. 1-8 *Clinical Ophthalmology*, vol. 4. (Harper & Row 1986).  
 "Cyclosporine Eyedrops for the Treatment of Severe Vernal Keratoconjunctivitis" BenEzra, et al. *Amer. J. Ophthal.* 101, 278-282 (1986).  
 "Diagnosis and Treatment of Tear Deficiencies" Lemp, Chapter 14, pp. 1-10. *Clinical Ophthalmology* vol. 4, Duane and Jaeger, Ed. (Harper & Row 1986).  
 "Diseases of the Cornea" by Grayson at pp. 334-367 (The C.V. Mosby Co. 1983).

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



1

4,027,274

2

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, mucous 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 Sjogren-like disease has been found in dogs with systemic lupus erythematosus.

Canine KCS is a common, chronic progressive, and 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 disease. It has been speculated in Kaswan et al., Am. J. Vet. Res. 46, 376-383 (1985), that most cases of canine KCS occur via autoimmune mechanisms.

The term autoimmunity is used to indicate immunologic self injury, but not a singular etiology. Autoir

3  
immune 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. 5

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) 10 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 15 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 20 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 25 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.

Ben Ezra 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) 35 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. 55

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 azathioprine. The systemic side effects of cyclosporine 60

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 eliminates 10 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 25 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 65

5

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,

6

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 tear 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: microdome, an artificial lipid membrane, polyvinylalcohol, or methylcellulose.

The cyclosporin is advantageously administered topically as an ophthalmic drop (solution or suspension) or ophthalmic ointment containing an 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.

7

4,007,042

8

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

4,037,342

9

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

After similar treatment for another two months, the Schürmer 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.

1 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 adminis-

10

tering 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.

• • • • •

45

50

55

60

65





US005474979A

**United States Patent** [19]

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

Ding et al.

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

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

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

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

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

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

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

[57] **ABSTRACT**

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

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.

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

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

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

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

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

**8 Claims, No Drawings**

5,474,979

1  
NONIRRITATING EMULSIONS FOR  
SENSITIVE TISSUE

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

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

As hereinabove noted, cyclosporin comprises a group of cyclic oligopeptides and the major component thereof is cyclosporin A ( $C_{62}H_{111}N_{11}O_{12}$ ) which has been identified along with several other minor metabolites, cyclosporin B through I. In addition, a number of synthetic analogs have been prepared.

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

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

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

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

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

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

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

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

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

2

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 viscosity 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



5,474,979

3

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®.

4

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%

5,474,979

5

-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

6

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.

\* \* \* \* \*

**1.5 EXCLUSIVITY  
CERTIFICATION**



**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


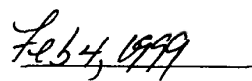
A Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine 0.05% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up To One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca

**ALLERGAN**

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.