CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-023

REVIEW # 4 **DATE REVIEWED:** 12/10/02

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	12/4/02	12/5/02	12/9/02

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME
Proprietary: RESTASIS
Established: cyclosporine
Code Name/#: 9054x
Chem.Type/Ther.Class: 3p

PHARMACOLOGY CATEGORY: Immunomodulator and anti-inflammatory agent
DOSAGE FORM: Emulsion
STRENGTHS: 0.05%
ROUTE OF ADMINISTRATION: Topical/ocular
DISPENSED: X Rx ___ OTC

PATENT INFORMATION:

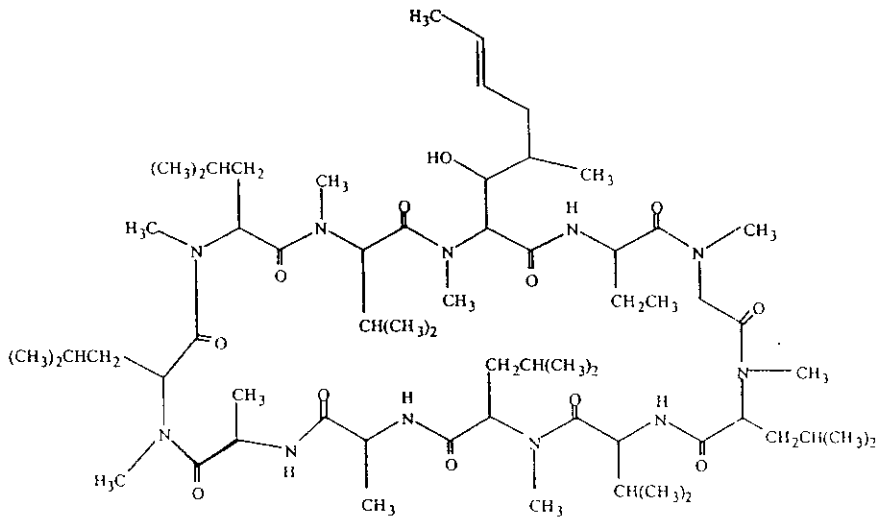
US 4,649,047
US 4,839,342
US 5,474,979

INDICATION: ———

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Molecular Formula
$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight
1202.6

Chemical Name & Structure
Cyclo{[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methyglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}



USAN Name:

Cyclosporine

Allergan Code Number (AGN#)

AGN 192371

Chemical Abstract Number

CAS 059865-13-3

Other Names

Cyclosporine A, cyclosporine, cyclosporin

SUPPORTING DOCUMENTS:

None

REMARKS:

In the chemist's review #3, the application was recommended for approval from chemistry, manufacture, and control standpoint. However due to clinical deficiencies, the NDA was not approved.

In the amendment dated 7/12/99, 7/29/99, and chemist's review # 2, Allergan agreed to monitor impurity [redacted], and [redacted] in the three validation batches, and submitted the results for evaluation, Allergan provides the results of such studies in this amendment.

On Dec. 4, 2002, a teleconference was held with Allergan's representatives discussing the impurities acceptance criteria, an agreement was reached to revise the drug product specification.

CONCLUSIONS & RECOMMENDATIONS:

The application is recommended for approval. All manufacturing facilities are in GMP compliance (as of 10/24/02) The application may be approved for 24 months and — — . expiration dates (when stored at 25° C) for the marketed package and — respectively.

cc:
Orig. NDA 21-023
HFD-550/Division File
HFD-550/Gorski
HF-550/Chemist/Tso
HFD-830/CChen
HFD-550/Ng
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee

Su C. Tso, Ph.D.
Chemist, HFD-550/830

Linda Ng, Ph.D.
Chemistry Team Leader, HFD550

6 Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Su Tso
12/13/02 01:44:01 PM
CHEMIST

Linda Ng
12/13/02 01:55:00 PM
CHEMIST
See Memo to File by LNg to complement this review

NDA 21-023

RESTASIS

cyclosporine Ophthalmic Emulsion, 0.05%

Allergan Inc.

Su C. Tso, Ph. D.

HFD- 550

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval. The approval is based on quality, safety, and efficacy of the dosage form.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active drug substance cyclosporine is a white to almost white powder. It is produced by [redacted] and is supplied by [redacted] Cyclosporine is an approved drug in NDA-50-573 and NDA 50-574. This NDA drug product is an [redacted] emulsion at 0.05% concentration manufactured at Allergan Inc. Waco, TX facility. The finished dosage form is packaged in LPDE unit-dose vial by [redacted] technique.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for [redacted], it is to be used one drop twice a day approximately 12 hours apart. The formulation contains no preservative in a unit dose vial, therefore the vial should be discarded after use.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval. This recommendation is based on the applicant's capability of manufacturing, and control of quality product (under GMP) for human consumption.

III. Administrative

A. Reviewer's Signature

Su C. Tso, Ph.D, HFD-550/830, *electronically signed in DFS*

B. Endorsement Block

Linda Ng, Ph. D., Chemistry Team Leader

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-023

REVIEW # 3 DATE REVIEWED: 3/22/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	9/3/99	9/7/99	9/14/99

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME
Proprietary: RESTASIS
Established: cyclosporine
Code Name/#: 9054x
Chem.Type/Ther.Class: 3p

PHARMACOLOGY CATEGORY: Immunomodulator and anti-inflammatory agent
DOSAGE FORM: Emulsion
STRENGTHS: 0.05%
ROUTE OF ADMINISTRATION: Topical/ocular
DISPENSED: X Rx ___ OTC

PATENT INFORMATION:

US 4,649,047
US 4,839,342
US 5,474,979

INDICATION: [redacted]

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

(1) Molecular Formula

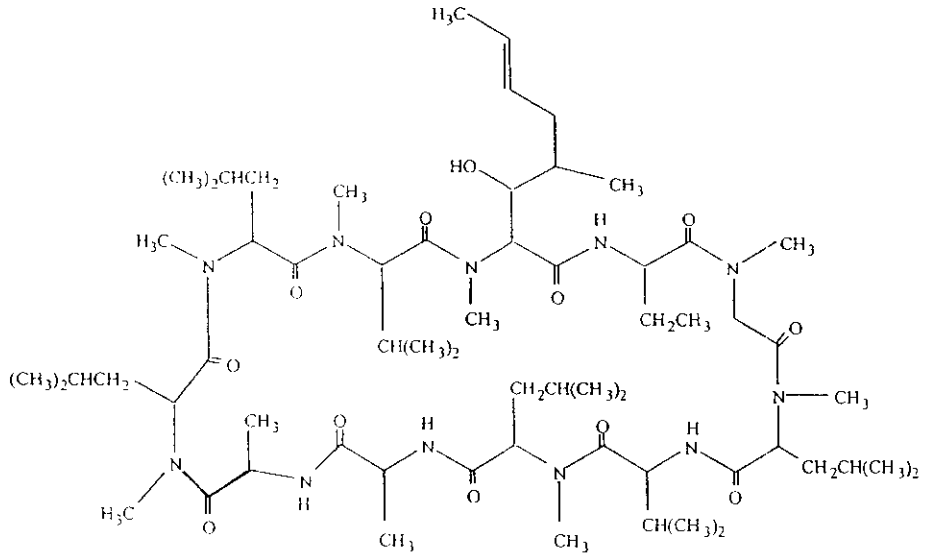
$C_{62}H_{111}N_{11}O_{12}$

(2) Molecular Weight

1202.6

(3) Chemical Name & Structure

Cyclo{[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methyglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}



(4) USAN Name
Cyclosporine

(5) Allergan Code Number (AGN#)
AGN 192371

(6) Chemical Abstract Number
CAS 059865-13-3

(7) Other Names
Cyclosporine A, cyclosporine, cyclosporin

SUPPORTING DOCUMENTS:

Chemist Review #1 and # 2

REMARKS:

Microbiological deficiencies have been resolved (refer to microbiologist review # 4 dated Feb. 2, 2000. The application was recommended for approval from chemistry, manufacture, and control standpoint. Method validation package was submitted on 9/3/99, but method validation has not been requested due to clinical deficiency.

CONCLUSIONS & RECOMMENDATIONS:

All manufacturing facilities are in GMP compliance (since 3/99). The application may be approved for [redacted] and [redacted] expiration dates (when stored at 25° C) for the marketed package [redacted] respectively.

/S/

Su C. Tso, Ph.D.
Chemist, HFD-550/830

/S/

Linda Ng, Ph.D.
Chemistry Team Leader, HFD550

cc:
Orig. NDA 21-023
HFD-550/Division File
HFD-550/Gorski
HF-550/Chemist/Tso
HFD-830/CChen
HFD-550/Ng
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-023

REVIEW # 2 **DATE REVIEWED:** 7/28/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	7/12/99	7/13/99	7/19/99
Amendment	7/26/99	7/27/99	7/28/99

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME
Proprietary: RESTASIS
Established: cyclosporine
Code Name/#: 9054x
Chem.Type/Ther.Class: 3p

PHARMACOLOGY CATEGORY: Immunomodulator and anti-inflammatory agent
DOSAGE FORM: Emulsion
STRENGTHS: 0.05%
ROUTE OF ADMINISTRATION: Topical/ocular
DISPENSED: X Rx __ OTC

PATENT INFORMATION:

US 4,649,047
US 4,839,342
US 5,474,979

INDICATION: [redacted]

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

(1) Molecular Formula

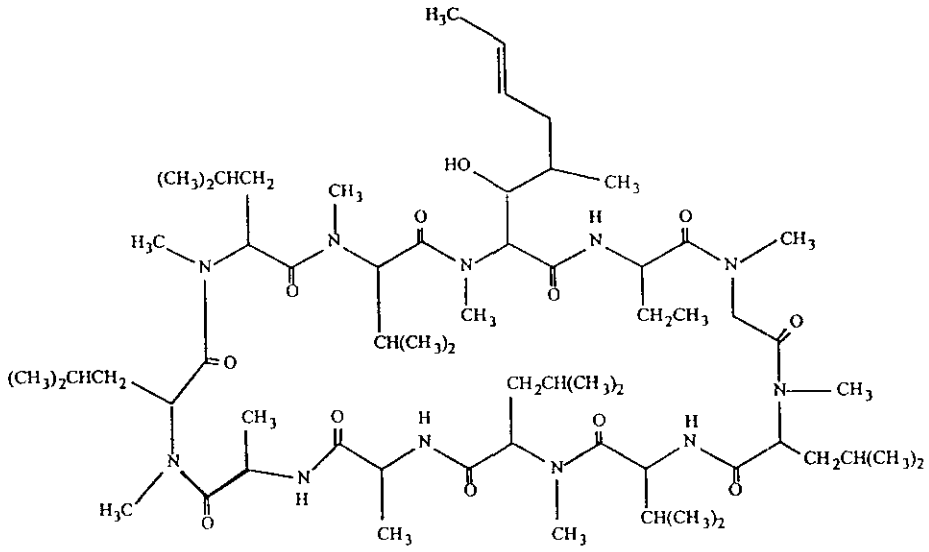
$C_{62}H_{111}N_{11}O_{12}$

(2) Molecular Weight

1202.6

(3) Chemical Name & Structure

Cyclo{[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methyglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}



(4) USAN Name
Cyclosporine

(5) Allergan Code Number (AGN#)
AGN 192371

(6) Chemical Abstract Number
CAS 059865-13-3

(7) Other Names
Cyclosporine A, cyclosporine, cyclosporin

SUPPORTING DOCUMENTS:

FDA phone/fax dated 6/9/99
FDA fax 7/23/99

REMARKS:

The first CMC reviewed was completed on 5/21/99. The recommendation was "approvable" with deficiencies. The applicant was informed of the deficiencies by fax on 6/9/99. The amendment of 7/12/99 is a response to the deficiencies cited in the fax. However, the responses are incomplete and unsatisfactory. A telecom was held with Elizabeth Bancroft of Allergan in the presence of Linda Ng, Ph. D. (chemistry team leader) on 7/21/99, followed by a fax dated 7/23/99. Amendment dated 7/26/99 addresses the overall deficiencies. This report summarizes the review of these two amendments. Method validation package will be requested.

CONCLUSIONS & RECOMMENDATIONS:

The responses to the deficiencies are satisfactory. Pending a satisfactory micro-review, the application is recommended for "approval" from a chemistry, manufacture, and control standpoint. All manufacturing facilities are in GMP compliance. The application may be approved for [redacted] and [redacted] expiration dates (when stored at 25° C) for the marketed package and [redacted] respectively.

Labeling agreed upon by the applicant should be confirmed later when the final labeling is submitted.

The applicant should be reminded of the [redacted]

cc:
Orig. NDA 21-023
HFD-550/Division File
HFD-550/Gorski
HF-550/Chemist/Tso
HFD-830/CChen
HFD-550/Ng
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee

/S/

Su C. Tso, Ph.D.
Chemist, HFD-550/830

/S/

Linda Ng, Ph.D.
Chemistry Team Leader, HFD550

10 Page(s) Withheld

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-023

REVIEW # 1 DATE REVIEWED: 5/21/99
First revision 6/5/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Pre-submission	12/9/98	12/10/98	12/14/98
Submission	2/24/99	2/25/99	3/2/99
Amendment	3/3/99	3/5/99	3/10/99
Amendment	3/18/99	3/19/99	3/25/99
Amendment	5/5/99	5/6/99	5/12/99
Amendment	5/10/99 (3)	5/11/99	5/13/99

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME
Proprietary: RESTASIS
Established: cyclosporine
Code Name/#: 9054x
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DOSAGE FORM: Emulsion
STRENGTHS: 0.05%
ROUTE OF ADMINISTRATION: Topical/ocular
DISPENSED: _X_ Rx __ OTC

PATENT INFORMATION:

US 4,649,047
US 4,839,342
US 5,474,979

INDICATION: ———

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

(1) Molecular Formula
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(2) Molecular Weight
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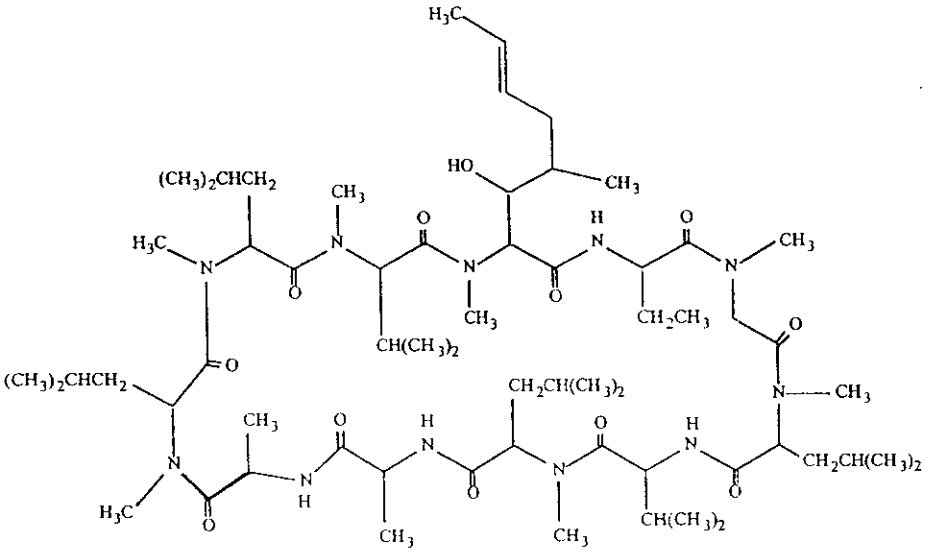
(3) Chemical Name & Structure

Cyclo{[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-



N-methyglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}

(4) USAN Name

Cyclosporine

(5) Allergan Code Number (AGN#)

AGN 192371

(6) Chemical Abstract Number

CAS 059865-13-3

(7) Other Names

Cyclosporine A, ciclosporin, cyclosporin

SUPPORTING DOCUMENTS:

NDA # 50-573, NDA # 50-574, IND 32,133, IND —, & IND —

DMF#	Type	Holder	Item/Component	Review Date	Status
	III	—		3/29/99	Acceptable

RELATED DOCUMENTS:

FDA e-mail dated: 12/20/99, 12/22/98, 4/21/99
FDA phone/fax dated 2/22/99, 4/7/99
FDA memo dated 3/19/99, 5/3/99, 5/5/99, 5/18/99

CONSULTS:

validation is consulted to microbiologist for review.

Trade name "RESTASIS" was reviewed and accepted by FDA N&L Committee at the IND phase III stage (March 1998). The acceptability of the trade name was confirmed on 4/21/99 by Dan Boring, Ph. D.

EER requested on 3/3/99. Pre-approval inspection for Waco, TX facility was conducted during the week of 4/26/99. No FDA form 483 was issued to the firm. Dallas District Office recommended "approval". All other manufacturing facilities are in GMP compliance as of 4/30/99.

REMARKS:

The CMC portion of this NDA was submitted as a Pre-submission on 12/9/99. In the pre-submission, Allergan requests the approval of 0.05% & cyclosporine emulsion. However in the formal submission dated 2/24/99, the sponsor , and requested the approval to market the 0.05% strength Since majority of the data support the application are derived from the 0.1% emulsion, therefore this report will include the review and discussion of cyclosporine emulsion of 0.1% and 0.05% strength.

Drug substance cyclosporine is manufactured by The chemistry, manufacture, and control of the drug substance are referenced to NDA & These NDAs are updated and current (FDA E-mail dated 12/22/99), they are adequate to support the manufacture of cyclosporine drug substance.

CMC information of the dosage form is provided in the pre-submission in vol. 1.1 to vol. 1.5. Additional CMC information is provided in the submission dated 2/24/99 in vol. 2.2, vol. 2.11, and vol. 2.12.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from a chemistry, manufacture, and control standpoint. All manufacturing facilities are in GMP compliance. The application may be approved for and expiration dates (when stored at 25° C) for the marketed package and , respectively. However, the final approval is pending for the satisfactory review of :

- validation by Microbiologist, and
- The responses from the applicant on the following deficiencies:

Deficiencies:

1. Please modify the drug product specifications as follows:

   a. Impurities should be controlled — and ——— in the regulatory specifications. The impurities should be subdivided as follows:

      Specified impurities:
      - Specified & identified for compounds with known structures
      - Specified and unidentified for compounds with unknown structures such as — and ——— The retention time for identification purpose can be used.
      - Total for the sum of the specified impurities

      Other unspecified or unknown impurities:
      - Other individual unspecified or unknown impurity
      - Other total unspecified or unknown impurities

      Total impurities for the sum of all impurities

   b. The — acceptance criteria should be tightened to reflect actual data.

   c. A second ID test (e.g., HPLC retention time) should be added to the specifications

2. Impurities testing should be included in the drug substance batches for annual retesting.

3. The post approval stability protocol should be revised to include impurities testing and a stability commitment statement, to be consistent with FDA Stability Guidelines, 1987, p.4.

4. The analytical method, HPLC ——— , should be revised to include testing for the — impurity. Supporting validation data for the analytical method should be submitted.

5. The — method for the ——— with supporting validation data should be submitted.

6. Labeling:

   Package insert:

   Under the DESCRIPTION section: vol 2.1 pg. 175
   - The inactive ingredients should be listed in the order of decreasing content
   - The values of osmolality and pH should be the same as those in the regulatory specifications.

Under the HOW SUPPLIED section:

The following package configuration statement should be included:

RESTASIS is packaged in unit-dose vials. Each unit-dose contains 0.4 mL fill in a 0.9 mL LDPE vial; 32 vials are packaged in a polypropylene tray with [redacted]

For the secondary packaging (the [redacted] label :

- On the PP thermoformed tray label, a [redacted] statement such as " [redacted] should be added.

7. Please provide microbiological data to support the [redacted] as stated in the [redacted] label.

(b)(1)

cc:
Orig. NDA 21-023
HFD-550/Division File
HFD-550/Chemist/Tso
HFD-830/CChen
HFD-550/Ng
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee
HFD-550/Gorski

Su C. Tso, Ph.D.
Chemist, HFD-550

(b)(1)

Linda Ng, Ph.D.
Chemistry Team Leader, HFD-550

43 Page(s) Withheld

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21023/000
Stamp: 25-FEB-1999 Regulatory Due: 25-AUG-1999
Applicant: ALLERGAN
2525 DUPONT DR
IRVINE, CA 926239534

Priority: 3P Org Code: 550
Action Goal: District Goal: 26-JUN-1999
Brand Name: RESTASIS(CYCLOSPORINE OPHTHALMIC EMULSIO
Established Name:
Generic Name: CYCLOSPORINE OPHTHALMIC EMULSION 0.05%
Dosage Form: EML (EMULSION, LOTION)
Strength: 0.05%

FDA Contacts:

L. GORSKI	(HFD-550)	301-827-2090	, Project Manager
S. TSO	(HFD-550)	301-827-2539	, Review Chemist
L. NG	(HFD-830)	301-827-2511	, Team Leader

Overall Recommendation:

ACCEPTABLE on 30-APR-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1643525
ALLERGAN INC
8301 MARS DR
WACO, TX 76712

DMF No:
AADA No:

Profile: SNI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-APR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 9610728
ALLERGAN PHARMACEUTICALS IR
CASTLEBAR RD
WESTPORT, COUNTY MAYO, EI

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date **10-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **04-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21023/000**
Priority: **3P** Org Code: **550**
Stamp: **25-FEB-1999** Regulatory Due: **09-NOV-2002**
Action Goal: District Goal: **10-SEP-2002**
Applicant: **ALLERGAN**
2525 DUPONT DR
IRVINE, CA 926239534
Brand Name: **RESTASIS(CYCLOSPORINE OPHTHALMIC EMULSIO**
Established Name:
Generic Name: **CYCLOSPORINE OPHTHALMIC EMULSION 0.05%**
Dosage Form: **EML (EMULSION, LOTION)**
Strength: **0.05%**

FDA Contacts:

L. GORSKI	(HFD-550)	301-827-2090	, Project Manager
S. TSO	(HFD-550)	301-827-2539	, Review Chemist
L. NG	(HFD-830)	301-827-2511	, Team Leader

Overall Recommendation:

ACCEPTABLE on 24-OCT-2002 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 30-APR-1999 by EGASM

Establishment: **1643525**
ALLERGAN INC
8301 MARS DR
WACO, TX 76712
DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-OCT-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **9610728**
ALLERGAN PHARMACEUTICALS IR
WESTPORT, COUNTY MAYO, EI
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-OCT-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-OCT-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-OCT-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Food & Drug Administration

Memorandum

Date: December 12, 2002

From: Linda Ng, Ph.D.,
Chemistry Team Leader, HFD-550

Subject: NDA 21-023, Restasis (cyclosporine ophthalmic emulsion) 0.05%, Allergan

To: The File

Via: Chi wan Chen, Ph.D.
Director, HFD-830

HFD-550 is finalizing the labeling for approval of NDA 21-023. Chemistry reviewer, Su Tso, commented on the labeling in chem review #1 dated June 16, 1999. This memo serves to complement chem review #4, which recommends approval from a chemistry, manufacturing and controls perspective.

Here is a summary of revisions recommended for the package insert, immediate container label, tray and carton labels.

Package Insert
Under Description,
1. Osmolality should have a lower case "o".
2. The pH should read "6.5 to 8.0" with removal of [redacted]
3. The amount as [redacted] should replace "0.05%" for cyclosporine.
4. The inactives list should be in order of glycerin, castor oil, polysorbate 80, carbomer 1342, purified water, and sodium hydroxide to adjust the pH.
5. Use comma instead of [redacted] for the listing of inactives.

Under How Supplied,
1. The type of lid should be included and read "..with aluminum peelable lid".
2. Replace the [redacted] with "to" for the Fahrenheit range.
3. Firm should justify the lower range of 15C for an emulsion and the " [redacted] ' statement. According to the freeze thaw data, product quality is maintained.

a. The storage statement is for 15° to 25°C. Please substantiate that prolonged exposure at 15°C is not detrimental to the emulsion.
b. Please provide justification for inclusion of the statement [redacted] " in the labeling

4. The word "vial" should be replaced by [redacted] " as the latter is the description for a sealed container as per C-DRR-00907, Package Type, CDER Data Standards Manual.

Tray Label

[redacted]

Tray Label and Carton

[redacted]

For ease of conveying comments to the firm, a comprehensive list that include other CMC comments is summarized in the Draft of Comments below. The package insert changes are incorporated by the Medical Reviewer and thus not included.

Other CMC comments.

1. The approved expiry for the product is 24 months and the [redacted]
2. Please include a date of completion for your commitment submitted in amendment dated December 4, 2002.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Ng
12/13/02 12:12:56 PM
CHEMIST
PM to convey comments to firm

Chi Wan Chen
12/13/02 12:21:34 PM
CHEMIST

MEMORANDUM

Department of Health & Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: May 18, 1999

FROM: William M. Boyd, M.D
Medical Officer, HFD-550

TO: Su C. Tso, Ph.D.
Linda Ng, Ph.D.
Asoke Muhkherjee, Ph.D.
Lori Gorski

THROUGH: Wiley Chambers, M.D.
Deputy Division Director, HFD-550

SUBJECT: [redacted], NDA 21-023 cyclosporine ophthalmic emulsion

Impurities control in cyclosporine emulsion

[redacted], were found during the stability studies of cyclosporine emulsion – one from the [redacted], and the other from an [redacted]

1) [redacted]

In protocols 192371-002 and-003, all 877 study subjects regardless of treatment group received drops from batches containing [redacted] for at least 6 months. Attached are Tables 9 and 16 from the Medical Officer's review that list all serious adverse events. None of these events was seen as attributable to the [redacted]

Non-serious adverse events were most commonly ocular. The most commonly reported adverse event, burning, was seen most frequently with the 0.1% cyclosporine concentration (21.6%) in protocol-002 and with the 0.05% concentration in protocol-003 (15.6%).

2) [redacted] of lot #11259

Lot #11259 was not used in clinical studies.

In a special study conducted on lot #11259 (submitted to NDA 5/10/99 BC), quantitation of the [redacted] substance indicated that the observed levels of the [redacted], are approximately [redacted] after 6 months of study at 25°C/40%RH and 40°C/20%RH. The sponsor presupposes the [redacted] is a [redacted] based on initial chromatographic information.

The sponsor estimates this would amount to an average of [redacted] /drop. The sponsor also finds the Total Daily Dose of the [redacted] is less than the 0.1% of the cyclosporine TDD and below the Threshold for Identification of Degradation Products as outlined in the ICH guideline on Impurities in New Drug Products.

Medical Officer's Conclusions:

The concentration of the [redacted] found in the lots used in the clinical trials for protocols –002 and –003 did not appear to cause any minor or significant adverse events during a six-month period.

The amount of the [redacted] that is found in the [redacted] method is acceptable.

Impurities control in cyclosporine emulsion

The impurities monitored in the stability protocol for NDA 21-023 are [redacted] Allergan purchases cyclosporine A from [redacted] According to [redacted] are both process impurities and potential degradents.

The sponsor indicates the limit of detection for cyclosporine related impurities is [redacted] and limit quantitation is [redacted] corresponding to [redacted] in the 0.05% formulation).

Input is requested on the pharmacological activity and toxicity of these impurities.

[redacted]

[redacted] was identified as a degradent in the original NDA [redacted] for

Medical Officer's Conclusions:

The [redacted] nonitored in the stability study for cyclosporine ophthalmic emulsion appear acceptable as [redacted] impurities and potential degradents. Based on their initially low concentrations and the low concentration of cyclosporine in the drug product, these impurities would not be expected to pose a toxicity problem and need not be monitored in the stability protocol.

cc
Orig. NDA 21-023
HFD-550/Division File
HFD-830/CChen
HFD-550/Ng
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Tso
HFD-550/Mukherjee
HFD-550/Gorski

Table 9 - Protocol-002

Serious Adverse Events Regardless of Causality: Patient Listing

Investigator/Patient	Age/Sex/Race	Investigator's Adverse Event Description	Days on Rx at Onset
0.05 % Cyclosporine Treatment Group			
1777-180	62 / F / C	intestinal fistula formation	56
2366-386	66 / F / C	difficulty breathing	24
		exacerbation of emphysema/COPD	185
2366-457	63 / F / C	bladder incontinence	blank
2366-479	42 / F / C	irregular uterine bleeding	177
2697-412	50 / F / C	dehydration	63
		pneumonia	13
2707-513	69 / F / C	acute CVA, left sided	48
		right sided paralysis	48
2709-234	52 / F / C	left femoral neck fracture	119
		left scaphoid fracture	119
2709-237	69 / F / C	atypical chest pain	40
0.01 % Cyclosporine Treatment Group			
0207-198	86 / F / C	bronchitis	161
		congestive heart failure	161
		pneumonia, persistent	161
		pneumonia, bilateral lower lobe	138
0207-201	78 / F / C	transient ischemic attack	33
0207-323	60 / M / C	fractured ankle, compound	9
2366-387	54 / F / C	malignant tumor, right kidney	155
2430-265	79 / F / C	hypotension	42
		lymphoma	44
2705-162	77 / M / C	MI	82
2706-178	81 / F / C	bowel and urinary incontinence	41
2706-329	58 / F / C	brain tumor, right frontal glioblastoma	161
2706-336	62 / F / C	pain in 2nd and 3rd digits of feet due to scleroderma	37
2707-128	87 / F / C	cellulitis, left leg	99
2707-435	58 / M / H	acute necrosis of the liver	40
		acute renal failure	40
		cholestasis	40
		malignant lymphoma	40
		septicemia	40
		thrombocytopenia	40
		vasculitis	40
2709-233	74 / F / C	CVA	131
Vehicle Treatment Group			
2366-388	87 / M / C	hematuria	57
		shortness of breath	37
2366-399	43 / F / C	severe 3 vessel coronary disease	23
2430-262	61 / F / C	cardiac arrest	95
		respiratory failure	93
		urosepsis	91
2697-228	84 / F / C	stress fracture, sacrum	162

Table 16 - Protocol-003
Serious Adverse Events Regardless of Causality: Patient Listing

Investigator/Patient #	Age/Sex/Race	Investigator's Adverse Event Description	Days on Rx at Onset
0.05 % Cyclosporine Treatment Group			
0200-228	60 / F / C	low platelet count	153
1438-565	59 / F / C	surgical repair of hearing loss, left ear	27
1796-131	78 / M / C	skin cancer, face	115
1838-126	82 / F / C	sudden cardiac death	58
2696-404	60 / F / C	bronchitis	74
		bronchitis/pneumonia	85
		coronary artery insufficiency	70
2696-420	61 / F / C	esophageal varix (Mallory-Weis)	147
		gastritis	147
		cirrhosis	blank
		pneumonia	151
2704-105	55 / F / C	seizure from sodium depletion	126
2710-578	65 / M / C	squamous carcinoma, esophagus	78
2821-538	69 / F / C	bowel obstruction	47
0.1 % Cyclosporine Treatment Group			
1438-528	71 / M / C	cardiac arrest	45
1485-263	60 / F / C	severe sinus infection	91
1796-242	49 / F / C	basal cell carcinoma	166
1838-322	57 / F / C	congestive heart failure	29
		fractured hip	65
		refractory, generalized edema	29
2696-406	54 / F / C	pustular skin eruptions c/w vasculitis	159
2704-104	72 / F / C	lymphoma – skin on back and lumbosacrum	87
2794-332	66 / F / C	lobar pneumonia	7
2798-599	74 / F / C	hospitalization due to foot infection	168
		hospitalization due to ankle fracture	186
Vehicle Treatment Group			
1838-325	39 / F / C	worsening of abnormal bleeding	100
2057-371	68 / F / C	left breast ductal carcinoma	129
2057-462	59 / F / C	ruptured appendix	179

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 3, 1999

FROM: Su C. Tso, Ph.D.
Chemist, HFD-830/550

TO: Wiley Chambers, M D.
Bill Boyd, MD
Asoke Mukherjee, Ph.D
Lori Gorski

THROUGH: Linda Ng, Ph.D.
Chemistry team leader, HFD-550/830

SUBJECT: Impurities control in cyclosporine emulsion, NDA 21-023

Cyclosporine is a cyclic polypeptide manufactured by. [redacted] A representative certificate of analysis shows the presence of [redacted] as impurities. Allergan purchases cyclosporine (also k own as cyclosporine A) from [redacted] has many NDAs with cyclosporine approved, among them are NDA [redacted], NDA [redacted] NDA [redacted], and NDA [redacted] All of these NDAs are approximately 10% cyclosporine solutions in corn oil and castor oil and others excipients. The impurities monitored in the stability protocol are [redacted] with limits of [redacted] and [redacted] respectively. According to [redacted] and [redacted] are both process impurities and potential degradants. The reported values in the stability program for NDA [redacted] and NDA [redacted] are [redacted], at 25 C up to 36 months for [redacted], and [redacted] for [redacted]

Allergan's 0.05% cyclosporine emulsion was an [redacted] emulsion while the cyclosporine is [redacted] In theory the cyclosporine i[redacted], and the stability of cyclosporine should parallel those of the cyclosporine [redacted] formulations. Allergan did study the stability of cyclosporine with respect to some of the process impurities but did not monitored for these [redacted] impurities due to lacking of impurity standards and the low concentration of cyclosporine in the finished dosage formulation. Allergan indicated that the limit of detection for cyclosporine related impurities is [redacted] and limit quantitation is [redacted] which corresponds to [redacted] in the 0.05% formulation

I need your input on the pharmacological activity and toxicity of these [redacted] impurities to determine the need of control these impurities in the stability of the finished dosage form.

The structures of [redacted] are attached for your reference. Your comments and advices are appreciated.

CC:
Orig. NDA 21-023
HFD-550/Division File
HFD-830/CChen
HFD-550/NG
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee
HFDD-550/Gorski
Filed: C:\review|ophthalm\21023impurities2

1 Page(s) Withheld

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 19, 1999

FROM: Su C. Tso, Ph.D.
Chemist, HFD-830/550 /S/

TO: Wiley Chambers, M D.
Bill Boyd, MD
Asoke Mukherjee, Ph.D
Lori Gorski

THROUGH: Linda NG, Ph.D.
Chemistry team leader, HFD-550/830 /S/

SUBJECT: [redacted], NDA 21-023

[redacted] were found during the stability studies of cyclosporin emulsion. One from the [redacted], and the other from the [redacted]

The [redacted] found from the [redacted] is identified as [redacted]. Its level [redacted]. The max. level found at product release is [redacted] and is [redacted] when stored at 25C/40%RH. The applicant claims that this impurity is present in [redacted], and at the max level found, it is non toxic. Please comment the toxicity of this impurity in the drug product. You may refer to the following CMC sections of the NDA (pre-submission dated 12/9/98) for your review.

VOLUME #	PAGE #
1.1	049
1.1	071
1.5	063
1.5	130

[redacted] was found during the stability study of the following batches: lots 11101, 11102, 11108, 11109, 11138, 11139, 11143, 11234, 11235, 11142, 11258, 11259, and 11260. These batches were used in clinical trial. Please refer to the Table on vol. 2.2, pgs. 2-019 to 2-025 (submission dated 2/24/99).

An [redacted] was detected in the [redacted] during the stability study of lot: 11259. The structure of this [redacted] has not been identified. Allergan believes it is a [redacted] component, since the same impurity was not found in the [redacted] studies of the [redacted] component. The estimated level is [redacted] at 3 month (40C/20%RH). Lot 11259 was not used in clinical study. At the present time, the nature of this impurity and max amount present is not known, it is my opinion that Allergen should consider replacing the [redacted] and [redacted]

Please advise.

CC:
Orig. NDA 21-023
HFD-550/Division File
HFD-830/CChen
HFD-550/NG
HFD-550/Boyd
HFD-550/Chambers
HFD-550/Mukherjee
HFDD-550/Gorski