

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-023

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-023

Trade Name Restasis Ophthalmic Emulsion, 0.05%
Generic Name cyclosporine ophthalmic emulsion
Applicant Name Allergan Inc. HFD-550
Approval Date December 23, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / X / NO / /
- b) Is it an effectiveness supplement? YES / / NO / X /
- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 50-563 Sandimmune

NDA # 50-715 Neoral

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application

contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: .. _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 192371-002

Investigation #2, Study # 192371-003

Investigation #3, Study # 192371-501

Investigation #4, Study # 192371-503

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|------------------|-----------|-----------------|
| Investigation #1 | YES /___/ | NO / <u>X</u> / |
| Investigation #2 | YES /___/ | NO / <u>X</u> / |
| Investigation #3 | YES /___/ | NO / <u>X</u> / |
| Investigation #4 | YES /___/ | NO / <u>X</u> / |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

| | |
|-------------|---------------|
| NDA # _____ | Study # _____ |
| NDA # _____ | Study # _____ |
| NDA # _____ | Study # _____ |

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|------------------|-----------|-----------------|
| Investigation #1 | YES /___/ | NO / <u>X</u> / |
| Investigation #2 | YES /___/ | NO / <u>X</u> / |
| Investigation #3 | YES /___/ | NO / <u>X</u> / |
| Investigation #4 | YES /___/ | NO / <u>X</u> / |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

| | |
|-------------|---------------|
| NDA # _____ | Study # _____ |
| NDA # _____ | Study # _____ |
| NDA # _____ | Study # _____ |

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 192371-002

Investigation #2, Study # 192371-003

Investigation #3, Study # 192371-501

Investigation #4, Study # 192371-503

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / X / NO / ___ / Explain: _____

Investigation #2

IND # YES / X / NO / ___ / Explain: _____

Investigation #3

IND # YES / X / NO / ___ / Explain: _____

Investigation #4

IND # YES / X / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

See electronic signature page

William M. Boyd, M.D.
Medical Officer

Wiley A. Chambers, M.D.
Deputy Division Director

cc:
HFD-093/Mary Ann Holovac
HFD-104/PEDES/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

William Boyd
12/23/02 12:22:32 PM

Wiley Chambers
12/23/02 03:42:02 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21023 Trade Name: RESTASIS(CYCLOSPORINE OPHTHALMIC EMULSIO

Supplement Number: Generic Name: CYCLOSPORINE OPHTHALMIC EMULSION 0.05%

Supplement Type: Dosage Form: EML

Regulatory Action: AE Proposed Indication: _____

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)

Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status -

Studies Needed -

Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Keratoconjunctivitis sicca is an extremely rare occurrence in the pediatric population.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LORI GORSKI

Signature LSI

Date 3/20/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 021023 **Trade Name:** RESTASIS(CYCLOSPORINE OPHTHALMIC EMULSIO
Supplement Number: 000 **Generic Name:** CYCLOSPORINE OPHTHALMIC EMULSION 0.05%
Supplement Type: N **Dosage Form:**
Regulatory Action: AE **COMIS Indication:** _____
Action Date: ~~8/3/99~~ 10/17/00

Indication # 1

Label Adequacy: Does Not Apply
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any): Keratoconjunctivitis sicca is an extremely rare occurrence in the pediatric population.

| | | | |
|--------------------|--------------------|---------------|-------------|
| <u>Lower Range</u> | <u>Upper Range</u> | <u>Status</u> | <u>Date</u> |
| 0 years | 16 years | Waived | |

This page was last edited on 10/17/00

Signature - LSI

Date 10/17/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

| | | | |
|---------------------------|--------------|-----------------------------|---|
| NDA/BLA Number: | <u>21023</u> | Trade Name: | <u>RESTASIS(CYCLOSPORINE OPHTHALMIC EMULSIO</u> |
| Supplement Number: | | Generic Name: | <u>CYCLOSPORINE OPHTHALMIC EMULSION</u> |
| Supplement Type: | | Dosage Form: | <u>EML</u> |
| Regulatory Action: | <u>AE</u> | Proposed Indication: | <u>_____</u> |

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO**COMMENTS:**

Keratoconjunctivitis sicca is an extremely rare occurrence in the pediatric population.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
 LORI GORSKI

Signature

LSA

Date

July 27, 1999

PEDIATRIC PAGE

NDA: 21-023

Stamp Date: February 24, 1999

Action Date: December 23, 2002

HFD-550 Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

Trade and generic names/dosage form: Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%

Applicant: Allergan, Inc

Therapeutic Class: Immunomodulator

Indication(s) previously approved: None

There is one indication for this application: To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Is there a full waiver for this indication? Yes

Please proceed to Section A.

Section A - Fully Waived Studies

Reason for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lori M. Gorski
Regulatory Project Manager

cc: NDA 21-023

HFD-950/ Terrie Crescenzi

HFD-960/Grace Carmouze

(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

**This is a representation of an electronic record that was signed electronically and
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/s/

Lori Gorski
12/24/02 10:40:20 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|--|----------------------|
| NDA 21-023 Approved December 23, 2002 | Efficacy Supplement Type SE- | Supplement Number |
| Drug: Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05% | Applicant: Allergan | |
| RPM: Lori Marie Gorski | HFD-550 | Phone # 301-827-2090 |
| Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | Reference Listed Drug (NDA #, Drug name): | |
| ❖ Application Classifications: | | |
| • Review priority | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority | |
| • Chem class (NDAs only) | New Formulation | |
| • Other (e.g., orphan, OTC) | N/A | |
| ❖ User Fee Goal Dates | March 9, 2003 | |
| ❖ Special programs (indicate all that apply) | <input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review | |
| ❖ User Fee Information | | |
| • User Fee | <input checked="" type="checkbox"/> Paid | |
| • User Fee waiver | <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other | |
| • User Fee exception | <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other | |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | |
| • This application is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | |
| • Exception for review (Center Director's memo) | N/A | |
| • OC clearance for approval | N/A | |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | <input checked="" type="checkbox"/> Verified | |
| ❖ Patent | | |
| • Information: Verify that patent information was submitted | <input checked="" type="checkbox"/> Verified | |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) | |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | <input type="checkbox"/> Verified | |
| ❖ Exclusivity Summary (approvals only) | December 23, 2002 | |
| ❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review) | N/A | |

| General Information | |
|--|---|
| ❖ Actions | |
| • Proposed action | (X) AP () TA () AE () NA |
| • Previous actions (specify type and date for each action taken) | 3 Previous AEs August 3, 1999, March 25, 2000, October 19, 2000 |
| • Status of advertising (approvals only) | (X) Materials requested in AP letter () Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (X) Yes () Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | (X) Nonc () Press Release () Talk Paper () Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | N/A |
| • Most recent applicant-proposed labeling | December 20, 2002 |
| • Original applicant-proposed labeling | February 24, 1999 |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) | DDMAC – December 13 & 20, 2002 ODS – December 11, 2002 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | N/A |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | N/A |
| • Applicant proposed | December 16, 2002 |
| • Reviews | See above |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | N/A |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | N/A |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | See package |
| ❖ Memoranda and Telecons | See package |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | October 24, 1996 June 4, 1996 |
| • Pre-NDA meeting (indicate date) | N/A |
| • Pre-Approval Safety Conference (indicate date; approvals only) | N/A |
| • Other | See package |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | July 21, 1999 |
| • 48-hour alert | N/A |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | N/A |

| Clinical and Summary Information | |
|---|--|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review) | |
| ❖ Clinical review(s) (indicate date for each review) | July 30, 1999 (2), March 10, 2000, October 3, 2000, October 16, 2000 (2), November 16, and December 16, 2002 (3), December 20, 2002, December 23, 2002 |
| ❖ Microbiology (efficacy) review(s) (indicate date for each review) | N/A |
| ❖ Safety Update review(s) (indicate date or location if incorporated in another review) | See above |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | December 24, 2002 |
| ❖ Statistical review(s) (indicate date for each review) | June 10, 1999, February 14, 2000 |
| ❖ Biopharmaceutical review(s) (indicate date for each review) | May 27, 1999 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review) | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | July 28, 1999 |
| • Bioequivalence studies | N/A |
| CMC Information | |
| ❖ CMC review(s) (indicate date for each review) | June 16, 1999, July 30, 1999, March 22, 2000, December 13, 2002 (2) |
| ❖ Environmental Assessment | |
| • Categorical Exclusion (indicate review date) | See CMC |
| • Review & FONSI (indicate date of review) | See CMC |
| • Review & Environmental Impact Statement (indicate date of each review) | See CMC |
| ❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review) | May 17, 1999, July 28, 1999 (2), February 23, 2000 |
| ❖ Facilities inspection (provide EER report) | Date completed: (X) Acceptable November 9, 2002 () Withhold recommendation |
| ❖ Methods validation | () Completed (X) Requested () Not yet requested |
| Nonclinical Pharm/Tox Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | July 15, 1999 |
| ❖ Nonclinical inspection review summary | N/A |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | N/A |
| ❖ CAC/ECAC report | N/A |

**This is a representation of an electronic record that was signed electronically and
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/s/

Lori Gorski
12/24/02 10:08:15 AM

21 Draft Labeling Page(s) Withheld

Office of Drug Safety

Memo

To: Lee Simon, MD
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

From: Marci Lee, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Lori Gorski
Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

Date: December 6, 2002

Re: ODS Consult 00-0232-1; Restasis (Cyclosporine Ophthalmic Emulsion); NDA 21-023

NOTE: This review contains proprietary and confidential information that should not be released to the public.***

This memorandum is in response to a November 19, 2002 request from your Division for a re-review of the proprietary name, Restasis. In our consult dated October 2, 2000 (ODS Consult #00-0232), the Division of Medication Errors and Technical Support (DMETS) did not have any objections to the use of the proprietary name, Restasis. However, DMETS' primary safety concerns involved the proposed labels, labeling, and packaging. DMETS made several recommendations to improve the safe use of Restasis in our initial review. We did not receive revised container labels or carton labeling and therefore cannot determine if the safety concerns from the initial review were considered (See Appendix A).

Based upon review of the revised package insert labeling, DMETS acknowledges that packaging the product in single-use containers and labeling them as single-use addresses the concern surrounding

the _____ described in Appendix A (A.2.a. and A.2.b.). However, it appears that 0.4 mL is more than the amount needed for a single dose. The estimated volume required for two drops based on 15-20 drops per milliliter is 0.1 – 0.13 mL. Therefore, there is a risk that patients may save the vial and use the remaining drug in the interest of saving money. The risks of using the drug beyond the single dose needs to be clearly communicated to practitioners, patients and caregivers especially since the product does not contain a preservative. Another way to minimize this risk is to use the least amount of overfill beyond the volume needed for two drops. Additionally, if space permits, we recommend that the terminology _____ be added to the labels and labeling.

Since the initial review, DMETS identified two additional proprietary names with potential for confusion with Restasis since we conducted our initial review. However, DMETS does not anticipate that these product names will cause confusion in the US marketplace at this time. See Table 1 for a side-by-side comparison of Restasis, Rescula, and _____. DMETS anticipates that although there are some similarities in the clinical context of use between Restasis and Rescula, these product names are different enough to coexist safely in the US marketplace. Additionally, the risk for confusion with Restasis and _____ is an issue to consider again when _____ is closer to approval.

Table 1. Comparison of Restasis, Rescula and _____

| Proprietary Name | Restasis | Rescula |
|-----------------------------|----------------------------------|---|
| Status | Pending NDA | Approved NDA |
| Established Name | Cyclosporine Ophthalmic Emulsion | Unoprostone Isopropyl Ophthalmic Solution |
| Sponsor | Allergan, Inc. | Novartis Ophthalmics |
| Indication | To increase tear production | Glaucoma |
| Dosage Strength | 0.05% | 0.15% |
| How Supplied | 0.4 mL single-use plastic vials | 5 mL |
| Usual Dose and Range | 1 drop BID OU | 1 drop BID OS/OD |
| Frequency of Administration | BID | BID |
| Route of Administration | EYE | EYE |
| Dosage formulation | OPHTH emulsion | OPHTH solution |
| Storage conditions | Room temp | Room temp |

In summary, DMETS has no objections to the use of the proprietary name Restasis but request consideration of the label and labeling comments outlined in this review for safer use of the product.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward. If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

NOTE: This review contains proprietary and confidential information that should not be released to the public. 2

APPENDIX A

Labeling, Packaging and Safety Related Issues from Initial ODS Consult # 00-0232

In the review of the draft labeling for Restasis, ODS has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, in the interest of minimizing potential user error.

A. PACKAGING CONFIGURATION/CONTAINER LABELING (0.4 mL containers)

1. We have safety concerns with the packaging of this product in a low-density polyethylene (LDPE) container. *In particular, these concerns relate to the labeling that appears on the flange.* To date, the sponsor has not submitted final copy of the paper label that will appear on the flange (personal communication, HFD-550). *We would strongly recommend that this labeling, once submitted, be reviewed by ODS.* This labeling *should be clear and distinctive*, since this type of packaging is being utilized in the manufacturing of other drug products. We also recommend that _____ since the product will be loosely stored in bins within the institutional setting.

Some of the products that are packaged in a like fashion include *nonprescription ophthalmic lubricants* and are *utilized by the same patient population*. These products include the following: AquaSite, Bion Tears, Celluvisc, Hypo Tears PF, Preservative Free Moisture Eyes, Refresh, Refresh Plus, OcuCoat PF, and Tears Natural Free. The corporate website for one product, Bion Tears, specifically states the following: "Preferred by severe dry eye patients (Sjogren's syndrome) over 4 other brands¹. *The possibility exists for a patient or health care provider to confuse one product with the other. The patient would then receive an underdose or overdose of Restasis in the process.*

Confusion between other non-ophthalmic products on the market in the U.S. that are packaged in LDPE containers has been documented in numerous reports to the FDA. These products are generally pulmonary inhalation solutions from various manufacturers and include the following generic substances: albuterol sulfate 0.083% inhalation solution, sodium chloride inhalation solution, and ipratropium bromide 0.02% inhalation solution. Although the volume of these products is generally larger (2.5 to 3 mL) than the single-use ophthalmic droppers proposed for Restasis (0.4 mL), *it is possible that these products could be confused with Restasis, or vice versa.*

2. The phrase ' _____ ' is quite restrictive and could be confusing to the user. Some clarification should be provided regarding the following issues.
 - a. How many doses or drops will each vial deliver? If more than two drops are deliverable, then the statement above seems to imply that ' _____ '

¹"Data on file, Alcon Laboratories, Inc." Source: http://www.alconlabs.com/us/eo/conditions/B1_BionTears.jhtml.

_____ according
to the statement above, if strictly adhered to by the user.

- b. In the interest of economy and conserving the drug product, it also seems likely that a patient will be inclined to use the remainder of the dropper, if the dosing is close to a 12-hour interval. Given the nature of cyclosporin therapy in an ophthalmic, preservative-free solution, can a local infection result from droppers used within, for example, 13 hours? *Because the _____ significant confusion and misuse seem likely.*

3. We have some concerns with the description of this package as a "vial".

4. The _____ is absent from the vial label (see 21 CFR 201.51).

B. CARTON LABELING (32-count tray)

C. PACKAGE INSERT LABELING

1. *We suggest substitution of the word 'μ' for the Greek "μL", as μ[L] is frequently mistaken for m[L], particularly with scripted instructions.*
2. *Under How Supplied, delete the phrase "fill in 0.9 mL LDPE vial", as inclusion of the empty container size frequently creates confusion over the actual contents and has resulted in medication errors on numerous occasions.*

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Denise Toyer
12/11/02 11:44:48 AM
PHARMACIST

Carol Holquist
12/11/02 11:48:17 AM
PHARMACIST

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: August 28, 2000

DUE DATE: October 1, 2000

OPDRA CONSULT #: 00-0232

TO: Karen Midthun, M.D.
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550

THROUGH: Lori Gorski, Project Manager
HFD-550

PRODUCT NAME: Restasis
(cyclosporin ophthalmic suspension,
0.5%)

MANUFACTURER: Allergan, Inc.
Irvine, CA 92612

NDA #: 21-023

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550), OPDRA conducted a review of the proposed proprietary name "Restasis" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name "Restasis". We have made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

151

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

151

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 19, 2000
NDA NUMBER: 21-023
NAME OF DRUG: Restasis (cyclosporin ophthalmic suspension, 0.05%)
NDA HOLDER: Allergan, Inc.
Irvine, CA 92612

I. INTRODUCTION

This consult was written in response to a request received on August 28, 2000 from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) for assessment of the tradename Restasis. This name was reviewed and found to be "Acceptable" by the FDA Labeling and Nomenclature Committee on April 2, 1998. On February 24, 1999, Allergan requested confirmation by the Division (HFD-550) regarding acceptability of the name Restasis.

Restasis (cyclosporin ophthalmic suspension, 0.05%) is indicated for _____

_____ The recommended dose is one drop twice a day in each eye, approximately 12 hours apart. The product will be supplied in 0.4 mL sealed unit-dose droppers, with 32 individual droppers packaged per tray. Once opened, each unit-dose dropper should be used _____

II. RISK ASSESSMENT

The medication errors staff of OPDRA conducted a search of several standard published drug product reference texts^{i,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to *Restasis* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted 3 prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Restasis. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Three product names were identified that were noted to have some sound-alike, look-alike qualities, relative to Restasis. These products were *Restoril* (7.5, 15, and 30 mg temazepam, oral capsule), _____, and *Retavase* (reteplase recombinant lyophilized powder for injection; thrombolytic agent). However, the Expert Panel believed that these *similarities are very slight* and, given the differences in dosage forms, route of administration, and dosing schedule, *confusion of any of these agents with Restasis seems unlikely*.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 90 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of *Restasis* with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for *Restasis* (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTIONS |
|--|---|
| <i>Inpatient:</i> Restasis i gtt ou q12h | <i>Outpatient:</i> Restasis, instill one drop in both eyes every 12 hours, dispense one with no refills |
| <i>Outpatient:</i> Restasis, #1, i gtt OU q12h. No refills. | |

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Please note that any and all information pertaining to _____ is protected by privacy laws and, therefore, is not releasable at this time. Redacting prior to FOI releases will be necessary.

2. Results

Results of this exercise are summarized below:

| Study | No. of participants | # of responses (%) | "Restasis" response | Other response |
|--------------------|---------------------|--------------------|---------------------|----------------|
| Written: Inpatient | 31 | 15 (48%) | 9 (60%) | 6 (40%) |
| Outpatient | 29 | 20 (69%) | 11 (55%) | 9 (45%) |
| Verbal: Outpatient | 30 | 16 (53%) | 12 (75%) | 4 (25%) |
| Total: | 90 | 51 (57%) | 32 (63%) | 19 (37%) |

Among participants in the 2 written prescription studies, 43% (15 of 35) of the respondents provided misspelled variations of the drug name. These incorrect responses were as follows: Reotans, Reostasis, Reotasis (n=3), Reotusis, Restaris (n=2), Restaxis, Restans, Restisa, Restisin, Restasia, Restasig, and Restasil.

Among the verbal prescription study participants, 25% (4 of 16) study participants interpreted the name incorrectly. The incorrect name interpretations were as follows: Respirase, Restacie, Restacius, and Restatis.

In all 3 studies, there was no overlap with existing U.S. drug product names.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Restasis", there were no existing drug product names identified by the Expert Panel or in the 3 prescription analysis studies conducted by OPDRA that were thought to have significant sound-alike or look-alike qualities relative to this name.

For these reasons, we do not object to the use of the proprietary name "Restasis".

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft labeling for Restasis, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, in the interest of minimizing potential user error.

A. PACKAGING CONFIGURATION/CONTAINER LABELING (0.4 mL containers)

1. We have safety concerns with the packaging of this product in a low-density polyethylene (LDPE) container. *In particular, these concerns relate to the labeling that appears on the flange.* To date, the sponsor has not submitted final copy of the paper label that will appear on the flange (personal communication, HFD-550). *We would strongly recommend that this labeling, once submitted, be reviewed by OPDRA. This labeling should be clear and distinctive, since this type of packaging is being utilized in the manufacturing of other drug products. We also recommend that the _____ since the product will be loosely stored in bins within the institutional setting.*

Some of the products that are packaged in a like fashion include *nonprescription ophthalmic lubricants* and are utilized by the same patient population. These products include the following: AquaSite, Bion Tears, Celluvisc, Hypo Tears PF, Preservative Free Moisture Eyes,

medication errors on numerous occasions.

IV. RECOMMENDATIONS

1. From a safety perspective, OPDRA has no objections to the use of the proprietary name "Restasis".
2. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

LS

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

LS

8/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-023

HFD-550: Division Files/Lori Gorski, Project Manager

HFD-550: Karen Midthun, Division Director

HFD-400: Jerry Phillips, Associate Director, OPDRA

HFD-400: Carol Pamer, Safety Evaluator, OPDRA

Electronic only cc:

HFD-002: Murray Lumpkin, Deputy Center Director for Review Management

HFD-400: Peter Honig, Director, OPDRA

HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC

HFD-430: Patrick Guinn, Project Manager, OPDRA

HFD-400: Sammie Beam, Project Manager, OPDRA

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2 Page(s) Withheld



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT - 4 1999

H. Dwight Cavanagh, M.D.
Department of Ophthalmology
University of Texas
Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75235-9057

Dear Dr. Cavanagh:

Between June 30 and July 19, 1999, Ms. Kelly J. Pegg, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #192371-003-02) of the investigational drug Cyclosporin 0.05% and 0.1% ophthalmic emulsions, performed for Allergan Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Pegg during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 1651049

Field Classification: NAI

Headquarters Classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

If Headquarters classification is a different classification, explain why:

cc:

HFA-224
HFD-550 Review Div. Dir.
HFD-550/ MO/Boyd
HFD-550/ PM/Gorski
HFD- 550/Doc. Rm. NDA # 21-023
HFD- 340 r/f
HFD- 344 c/r/s GCP file#01009
HFD- 344/Carreras
HFR-SW150/Thornburg
HFR-SW1540/Martinez
HFR-SW1540/Pegg

r/d:JAC/8/24/99
final: bc/9/29/99

Note to Rev. Div. M.O.

This investigator enrolled 12 subjects in the study. Three subjects were D/C. Seven subjects were rolled over to the extension study. The D.O. investigator examined all subject records including CRFs, subjects files, and sponsor supplied tabulations. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

Food and Drug Administration
Rockville MD 20857

JUL 28 1999

Kenneth Sall, M.D.
Sall Eye Surgery Center
9604 E. Artesia Blvd., Suite 203
Bellflower, California 90706

Dear Dr. Sall:

Between June 8 and 10, 1999, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #192371-002-003) of the investigational drug Cyclosporin 0.05% and 0.1% ophthalmic emulsions, performed for Allergan Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Koller during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,



 Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practices II, HFD-45
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Gorski, Lori M

From: Williams, Rebecca
Sent: Thursday, December 12, 2002 5:12 PM
To: Gorski, Lori M; Rumble, Warren F
Cc: Williams, Rebecca
Subject: Restasis PI

Hi Lori -

Thank you for including DDMAC in the approval process. Unfortunately, the short time frame makes it difficult to provide very detailed comments, but I have provided a number of comments/questions directly in the text of the document you e-mailed us. If you have any questions please feel free to contact me tomorrow. I will be in the office all day.

Becky
7-3902



121202
stasis PI CONS.c

5 Draft Labeling Page(s) Withheld

TELE-CON MEETING MINUTES

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

MEETING DATE: May 22, 2002

TIME: 2:00 PM EST

NDA: 21-023

DRUG: Restasis cyclosporine ophthalmic emulsion

SPONSOR/APPLICANT: Allergan, Inc.

MEETING TYPE: Follow-up call to sponsor after Review Team Meeting of submission to NDA dated April 23, 2002

FDA Attendees:

William Boyd, Medical Officer
Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
Jennifer Harris, Medical Officer
Lisa Hubbard, Clinical Reviewer
Raphael Rodriguez, Project Manager

Allergan Attendees

Elizabeth Bancroft, Regulatory Affairs
Peter Kresel, VP Regulatory Affairs
Scott Whitcup, Clinical Research
Thomas Lin, Statistician
Katherine Stern, Statistician

BACKGROUND: Allergan submitted NDA 21-023 in February 1999, and to date have been issued three approvable (AE) letters. A submission dated April 23, 2002, came in intended as a full response our last AE. At an internal team meeting regarding the submission it was determined there was not enough information in the submission for a full response. This call was to notify the sponsor of the deficiencies and that the review clock has not been started.

The following are deficiencies/issues conveyed to the sponsor based on the April 23, 2002, submission.

1. The April 23, 2002, submission is not considered a full response to the Approvable letter. Thus, this submission is not major amendment, and the review clock will not be started.
2. Please provide the Division with full study reports on Study 192371-503.
3. Please provide the Division with the full study reports for the Ocular Surface Disease Index (OSDI) Study. If this information has previously been submitted to the NDA please provide the date and location where the full Study Report can be found.
4. Please conduct the same analyses (patients who achieved an increase in Schirmer wetting scores equal to or greater than 10 mm at the 6 month time point) that were submitted in the April 23, 2002, submission on Study 192371-501.
5. Please provide correlation coefficients for the analyses performed on the OSDI and 192371-503 databases and submitted in the April 23, 2002, submission. Please include confidence intervals

6. The current Division policy is that one sign and one symptom should have statistically significant findings before an approval is granted. This current submission is asking the Division to consider replication of only one sign for approval. The sponsor was told that the Division has not made a determination that one replicated sign could be sufficient for approval.

The meeting ended amicably.

MEETING MINUTES

Lori Gorski – Project Manager
Wiley Chambers – Deputy Division Director

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

/s/

Wiley Chambers

8/7/02 09:07:41 AM

T-CON MEETING MINUTES

MEETING DATE: 1/17/01

TIME: 3:00 PM EST

NDA: 21-023

Meeting Request Submission Date: 1-08-01

Date Sponsor Requested: ASAP

Briefing Document Submission Date: 1-08-01

DRUG: Cyclosporine

SPONSOR/APPLICANT: Allergan

MEETING TYPE: type C

FDA PARTICIPANTS:

Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
Bill Boyd, Medical Officer
Jennifer Harris, Medical Officer
Lucious Lim, Medical Officer

INDUSTRY PARTICIPANTS:

Elizabeth Bancroft, Regulatory Affairs
Peter Kresel, Vice President, Clinical
Scott Whitcup, Clinical
Thomas Lin, Statistician
Harold Jensen,
Katherine Stern, Statistician

MEETING OBJECTIVES: discuss draft clinical protocol on cyclosporine

BACKGROUND INFORMATION: A confirmatory phase 3 study is required on cyclosporine.

MEETING DISCUSSION ITEMS:

Allergan will pool the study results from 002 and 003 previously completed and submitted to NDA 21-023. The division advised that a confirmatory study is required for the application. Previous studies required < 5mm on Schirmers, Allergan asked if this could be increased to 8 mm – the Division has no problem with that.

Allergan would like to use some of the same investigators as in the previously completed and submitted studies – the Division responded that the farther away they are from the previously used investigators the better. The majority of the investigators should not be reused, and the ones reused should not carry the results of the study outcome. Absolutely no patients should be reused.

Allergan asked if a ~~_____~~ in the composite score of itching and blurred vision is clinically meaningful. The Division disagreed and prefers that mean changes go to zero to represent a meaningful result. The blurred vision stratification in the draft is acceptable.

The Division noted no other specific comments.

LSI
Lori Gorski
Project Manager

LSI
Concurrence Chair: Wiley Chambers, M.D.
Deputy Division Director

MEETING MINUTES

6. The Agency deferred comment on whether the Ocular Surface Disability Index is acceptable as a primary efficacy endpoint for Phase 3 until the full report, data, and analysis are provided as an IND amendment. The timeframe for review of the OSDI validation will depend on the current workload when the data come in. However 150 patients is appropriate for validation. If the OSDI is not acceptable, Allergan will use the facial expressions scale.
7. The microbiology results on page 8 were in dry eye patients. A copy of corrected information was provided at the meeting. This information and a list of the organisms used will be submitted in an IND amendment.

Joanne M. Holmes

cc:

IND 32,133

HFD-550 Div files

HFD-105/ODE V/Weintraub

HFD-105/ODE V/Walling

HFD-550/Acting Div Dir/Chambers

HFD-550/MO/Bull/1-24-97

HFD-550/MO/Ludwig

HFD-550/Clin Rev/Holmes/1-24-97

HFD-550/SPMS/LoBianco

HFD-725/Stat TL/Leung/1-15-97

HFD-550/Proj Mgr/c

HFD-550/Proj Mgr/c

LS

LS

RECORD OF A MEETING

Date: April 24, 1997
IND: 32,133
Subject: Chemistry, Manufacturing & Controls
Drug: Cyclosporine Ophthalmic Emulsion
Indication: _____
Sponsor: Allergan, Inc.
Allergan Attendees: John Kent, Steve Rucknick, Elizabeth Bancroft, Orest Olejnik
FDA Attendees: Wiley Chambers, Joanne Holmes, D'Annie Gunter, Lissante LoBianco,
Mark Seggel, Su Tso, Allan Fenselau, Hasmukh Patel

1. Allergan stated that based on their developmental work, they did not see a need for regulatory specifications for related substances in the finished drug product.

The Agency stated that all regulatory specifications were applicable to ophthalmics, including globule size distribution and impurities. Allergan was also advised that the ICH guidelines do not include ophthalmics.

Allergan proposed to monitor the registration stability product for all time points using both Method 1 and Method 2 for one year. If no major differences between the Methods occurred, then all subsequent studies, stabilities, and commercial product release would continue using only Method 2. Allergan will provide data on both methods for the same lots for review.

The Agency stated that the regulatory requirements would remain applicable. FDA would not agree to not use Method 1 because it displays degradation products which are not observed with Method 2.

2. Based on emulsion characteristics and processing factors, Allergan proposed that a regulatory specification for globule size in the finished drug product is not required.

The Agency stated that regulatory specifications for globule size in the finished drug product is required. Allergan needs to display batch to batch size from time zero until the end of shelf life. It was suggested that Allergan set a limit of no more than _____ since particle size affects availability and changes in globule size may indicate instability. A specification should be set by the time of the NDA submission.

3. Additional Issues

- a. Glycerin USP - make sure to check for _____ impurities.
- b. Allergan will provide a copy of the DMF on _____. There was concern about the presence of _____.
- c. Allergan may utilize EP grade castor oil, as long as they supply a USP Certificate of Analysis, or show that it meets or exceeds USP tables.

IND 32,133
Minutes Con't
Page 2

cc:

HFD-550/IND32,133

HFD-550/Division Files

HFD-550/Acting Div. Dir/Chambers 7/1/97 IS1

HFD-550/SPMS/LoBianco

HFD-550/Clin Rev/Holmes 5/20/97, 6/12/97

HFD-550/PM/Gunter 5/22/97 IS1

HFD-550/Chem TL/Patel

HFD-550/Chem/Tso 5/23/97, 6/15/97

HFD-550/Chem/Fenselau 5/23/97, 6/11/97

HFD-530/Seggel

Drafted by: dg/April 25, 1997/ind32133.min

JUN 4 1996

Holmes
530

RECORD OF A MEETING

Date: June 4, 1996
IND: IND 32,133
Subject: End of Phase 2
Drug: Cyclosporine Ophthalmic Emulsion
Indication: _____
Sponsor: Allergan

Between members of Allergan: Michael Stern, Elizabeth Bancroft, Brenda Reis, Katherine Stern, and James Wang

and FDA: Michael Weintraub, Mary Jane Walling, Wiley Chambers, Jose Carreras, Jonca Bull, Regina Joyce, Hoi Leung, and Joanne Holmes

The discussion addressed the issues presented in the May 23, 1996, briefing package.

1. It is acceptable to treat 300 patients on study drug (150 per group in each protocol).
2. The data showed a vehicle effect for dryness. They did not support 0.1% as the best dose to proceed with in Phase 3 trials. It seemed to show efficacy on the objective criteria, but not on subjective. It was recommended that at least 1 trial needs a third arm, perhaps 0.05%, to confirm that there is not a lower dose with equal effectiveness. Additional safety data will also be obtained.
3. A responder is a patient who goes to zero in both signs and symptoms. To show efficacy, Allergan must determine before beginning the study whether they will seek to show a 1 unit (grade) difference between active and vehicle groups or a statistical difference of a higher percentage of patients cured between active and vehicle.
4. The Ocular Surface Disability Index must be validated to be used as a subjective measure, or another method should be used.
5. A 6-month study with visits at 1, 2, 3, and 6 months, a 4-week follow-up, and a 1 year open label period is acceptable. Another option is to put patients in a controlled, adverse environment and evaluate for dry eye with baseline, post-therapy, and off-treatment biopsies.

Joanne M. Holmes

cc: IND 32,133
HFD-550 Div files
HFD-105/Office Dir/Weintraub
HFD-105/Spec Asst/Walling
HFD-550/Acting Div Dir/Chambers/11-7-96
HFD-550/MOs/Bull/Carreras/Ludwig
HFD-550/Clin Rev/Joyce
HFD-725/Stat TL/Leung
HFD-550/Proj Mgr/Holmes/8-30-96

JS

5 Page(s) Withheld