CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-493 SUPPL #
Trade Name Zymar Generic Name (gatifloxacin ophthalmic solution 0.3%)
Applicant Name Allergan HFD-550
Approval Date

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/

If yes, what type(SE1, SE2, etc.)?

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?

3 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 # 21-061 Tequin

NDA # 21-062 Tequin

NDA # [redacted] _____

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 / _X_/

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 /___/

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 # SPCL-GFLX 3/01

Investigation #2, Study # SPCL-GFLX 3/02

Investigation #3, Study #

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 /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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 # _SPCL-GFLX 3/01_

Investigation #_2_, Study # _SPCL-GFLX 3/02_

Investigation #__, Study #

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:

(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: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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Jennifer Harris
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Wiley Chambers
3/28/03 12:21:55 PM

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-493 **Stamp Date:** May 30, 2002 Action Date: March 28, 2003

HFD -550 **Trade and generic names/dosage form:** Zymar (gatifloxacin ophthalmic solution) 0.3%

Applicant: Allergan, Inc. **Therapeutic Class:** anti-infective

Indication(s) previously approved: – there are no previously approved indications for the ocular dosage form

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: _ the treatment of bacterial conjunctivitis caused by designated susceptible organisms

Is there a full waiver for this indication (check one)?

❑ Yes: Please proceed to Section A.

XXX No: **Please check all that apply:** ____**Partial Waiver** ____Deferred XXX Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg_____	mo._____	yr._1___	Tanner Stage_____
Max_____	kg_____	mo._____	yr._16__	Tanner Stage_____

Comments:

If there are additional indications, please proceed to 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, Project Manager

cc: NDA 21-493
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

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/s/

Lori Gorski
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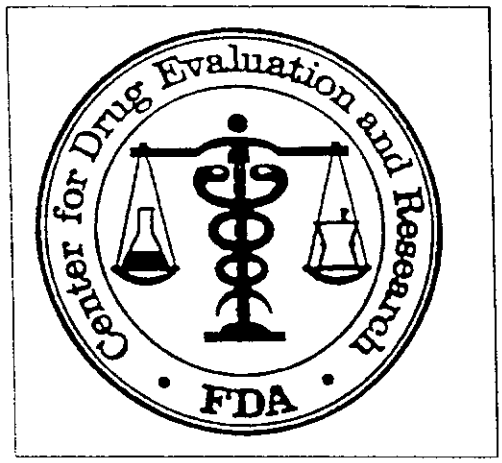

From: Libaniel Rodriguez. Ph.D.
Review Chemist

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

Phone 301-827-2069
Fax 301-827-2531

Date: February 25. 2003

To:

Name: Elizabeth Bancroft
Company: Allergan,Inc.
City: Irvine State:CA
Phone #: 714 246 4391

FAX #: 714 246 4272

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2069MMEDIATELY if re-transmission is necessary.

If you have any question about this information request, please call me.

Libaniel Rodriguez

February 25, 2003

NDA 21-493 ZYMAR™(gatifloxacin ophthalmic solution) 0.3%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

DRUG PRODUCT

1. Please provide a statement that the beige cap complies with the AAO color scheme.
2. Please submit a one-time droplet size study for the container closure system.
3. Revise and submit the drug product specification to include the proposed acceptance criterion for ——— nd correct errors in the Identification tests for benzalkonium chloride and ———

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/s/

Libaniel Rodriguez
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Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Elizabeth Bancroft, Allergan	**From:** Lori Gorski, Project Manager
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone: 714-246-4391	**Phone:** 301-827-2521
Pages: 1 including cover sheet	**Date:** February 13, 2003
Re: Gaifloxacin clinical comments from NDA 21-493	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Elizabeth,

The following are preliminary questions from the clinical reviewer for gatifloxacin.

1. Study 3/02 had a significant number of patients "lost to follow-up." Please describe the methods used to locate these patients and provide an exploratory analysis of the potential impact on the study results.

Please respond with a submission to the NDA submission.

Call me if you have any questions.

Thanks,

Lori Gorski

/S/

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/s

Lori Gorski
2/13/03 03:55:01 PM
CSO

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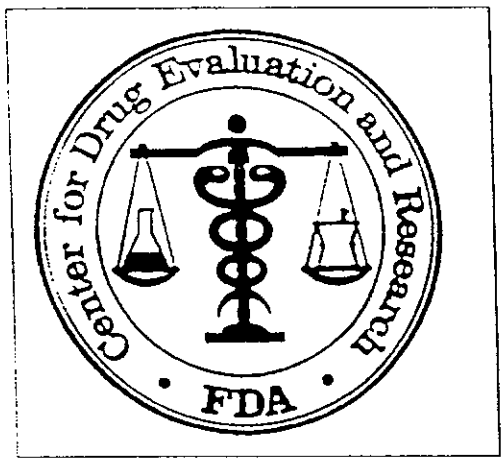

From: Libaniel Rodriguez
Review Chemist

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

Phone 301-827-2069
Fax 301-827-2531

Date: February 5, 2003

To: Name: Elizabeth Bancroft
Company: Allergan,Inc.
City: Irvine State:CA
Phone #: 714 246 4391

FAX #: 714 246 4272

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2069MMEDIATELY if re-transmission is necessary.

If you have any question about this information request, please call me.

Libaniel Rodriguez

February 5, 2003

NDA 21-493 [redacted] **4(gatifloxacin ophthalmic solution) 0.3%**

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. Please submit updated stability data at 25°C for the three primary registration batches and for the Waco and Westport commercial lots.
2. In your response of September 23, 2002, answer to request number 3, you deleted method [redacted] 3 for [redacted] and replaced it with method [redacted] for the same test. Please provide numerical data obtained with method [redacted] for the registration and commercial batches.
3. Please submit results and actions taken for any [redacted] investigations under this NDA.
4. For the drug product specification, tighten the [redacted] acceptance criterion to reflect actual data.
5. The drug substance manufacturing facility in Okaya could not be inspected. KYORIN Pharmaceutical Co., Ltd. notified FDA that manufacturing of the drug substance was recently transferred from their Okaya plant to their Noshiro plant. Please clarify.

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/s

Libaniel Rodriguez
2/5 03 10:15:38 AM
CHEMIST

Linda Ng
2/5 03 10:21:46 AM
CHEMIST

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Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 24, 2003

NDA NUMBER: 21-493

NAME OF DRUG: Zymar (Gatifloxacin Ophthalmic Solution) 0.3%

NDA HOLDER: Allergan, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) for assessment of the tradename "Zymar", regarding potential name confusion with other proprietary or established drug names. The sponsor submitted a prior name, ——— which DMETS found unacceptable on December 24, 2002 (see ODS Consult 02-0135).

PRODUCT INFORMATION

"Zymar" is the proposed proprietary name for gatifloxacin ophthalmic solution and is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of organisms (*Staphylococcus aureus*, ——— *Staphylococcus epidermidis*, *Streptococcus mitis*, ——— *Streptococcus pneumoniae* ——— *Haemophilus influenzae*, ——— . Gatifloxacin has antibacterial action that results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. The recommended dosage regimen for "Zymar" is instill one drop every two hours in the affected eye(s) while awake on days one and two, up to eight times daily. On days three through five, instill one drop up to four times daily while awake. "Zymar" will be available as 2.5 mL and 5 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Zymar" 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 the U.S. Patent and

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database[4] and the data provided by [redacted] Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Zymar". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and 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.

1. The panel had look-alike concerns with *Zyban, Zyvox,* and *Zymine* as well as sound-alike concerns with *Vimar* and *Chymar*. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name "Zymar" with regard to promotional claims.

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Table 1

Product Name	Dosage form(s); Generic name	Usual adult dose*	Other**

[4] WWW location http://www.uspto.gov.

[5] Data provided by [redacted]

Zymar	Gatifloxacin (Rx) Ophthalmic Solution: 0.3% (2.5 mL and 5 mL)	Days 1 and 2: Instill one drop every 2 hours in the affected eye(s) while awake, up to 8 times daily. Days 3 through 5: Instill one drop up to 4 times daily while awake.	
Zyban	Bupropion Hydrochloride (Rx) Tablet (sustained-release): 150 mg	1 tablet twice a day	LA
Zyvox	Linezolid (Rx) Tablet: 400 mg and 600 mg Injection: 2 mg/mL (100, 200, and 300 mL bags) Powder for Reconstitution: 100 mg/5 mL (240 mL)	*Vancomycin-resistant Enterococcus faecium infections, nosocomial pneumonia, complicated skin and skin-structure infections, and community-acquired pneumonia* 600 mg IV or oral every 12 hours. *Uncomplicated skin and skin-structure infections* 400 mg oral evy	LA
Zymine	Triprolidine Hydrochloride (Rx) Liquid: 1.25 mg/5 mL (15 and 473 mL)	10 mL every 4 to 6 hours, not to exceed 40 mL in 24 hours.	LA
Vimar	Multivitamin without Minerals (Last Recorded Sale: 1997)	N/A	SA
		N/A	SA

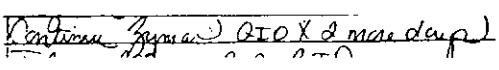
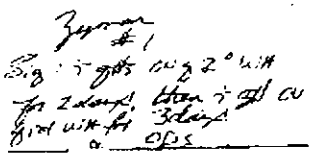
*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Zymar" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Zymar" (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review.

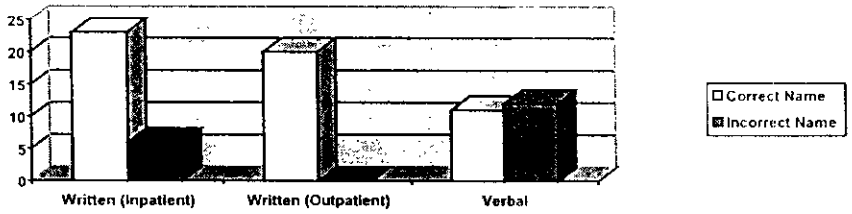
After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: 	*Outpatient Rx:* Zymar, number 1. Instill 1 drop into both eyes every 2 hours while awake for 2 days, then instill 1 drop into both eyes 4 times a day while awake for 3 days.
Outpatient Rx: 	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Zymar"	Incorrectly Interpreted
Written Inpatient	35	29 (83%)	23 (79%)	6 (21%)
Written Outpatient	32	20 (63%)	20 (100%)	0 (0%)
Verbal: Outpatient	39	23 (59%)	11 (48%)	12 (52%)
Total	106	72 (68%)	54 (75%)	18 (25%)



Among the written inpatient prescriptions, 6 (21%) out of 29 respondents interpreted "Zymar" incorrectly. Incorrect interpretations included *Zyman* (2 respondents, 7%), *Zumar* (1 respondent, 3%), *Zynia* (1 respondent, 3%), *Zyma* (1 respondent, 3%), and *Zymiar* (1 respondent, 3%).

Among the written outpatient prescriptions, none of the respondents interpreted "Zymar" incorrectly.

Among the verbal outpatient prescriptions, 12 (52 %) out of 23 respondents interpreted "Zymar" incorrectly. Incorrect interpretations included *Zymor* (3 respondents, 13%), *Zymore* (3 respondents, 13%), *Zymox* (2 respondents, 9%), *Zimar* (1 respondent, 4%), *Zynar* (1 respondent, 4%), *Xymar* (1 respondent, 4%), and *Zimof* (1 respondent, 4%).

None of the respondents interpreted "Zymar" as an existing U.S. marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Zymar", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The proprietary names that were of concern are *Zyban*, *Zyvox*, and *Zymine*.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that "Zymar" can be confused with existing drugs on the U.S. market. All of the interpretations from the verbal and written prescription studies were phonetic/misspelled variations of the drug name "Zymar".

DMETS had look-alike concerns between the proprietary names *Zyban* and "Zymar". *Zyban* contains bupropion hydrochloride and is indicated as an aid to smoking cessation treatments. Both proprietary names begin with "Zy" and the last two letters in each name can look similar when scripted ("an" and "ar"). However, the upstroke of the "b" in *Zyban* may distinguish *Zyban* from "Zymar" (see below). Even though both products are available in one strength, they have different dosage forms (tablet vs. ophthalmic solution), different route of administration (oral vs. ophthalmic), and different directions of use (one tablet twice a day vs. one drop every 2 hours in the affected eye(s) while awake, up to 8 times daily, on days 1 and 2, and instill one drop up to 4 times daily while awake on days 3 through 5). Since the directions of use for "Zymar" are cumbersome, they would likely be written out on a prescription or written as "use as directed". However, the differences between the scripted names as well as the above differences would decrease the potential risk of medication errors occurring between these two products.

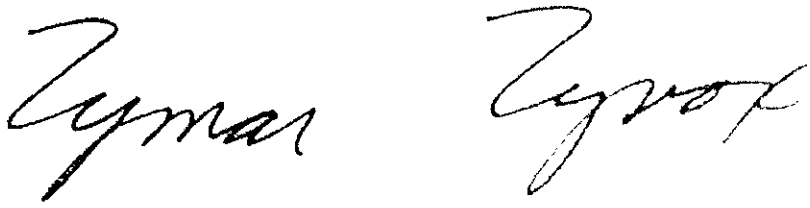
Writing Sample:

Zymar

Zyban

DMETS had look-alike concerns between the proprietary names *Zyvox* and "Zymar". *Zyvox* contains linezolid and is indicated for the treatment of various infections caused by certain susceptible bacteria. Both proprietary names begin with "Zy" and the "vo" in *Zyvox* can sometimes look similar to the "ma" in "Zymar", depending on how they are written. The first downstroke of the scripted "x" in *Zyvox* can look similar to a scripted "r"; however, the second downstroke of the "x" may differentiate it from a scripted "r" (see page 7). *Zyvox* and "Zymar" differ in dosage form (tablet, powder for reconstitution, and injection vs. ophthalmic solution), different strengths (400 mg, 600 mg, 100 mg/5 mL (in 240 mL), and 2 mg/mL (100, 200, and 300 mL bags) vs. 0.3% (2.5 mL and 5 mL)), different number of strengths (400 mg, 600 mg, 100 mg/5 mL, and 2 mg/mL vs. 0.3%), and different directions of use (400 mg-600 mg twice a day vs. one drop every 2 hours in the affected eye(s) while awake, up to 8 times daily, on days 1 and 2, and instill one drop up to 4 times daily while awake on days 3 through 5). Since *Zyvox* tablets are available in two strengths, the strength would likely be indicated on a *Zyvox* tablet prescription whereas "Zymar" is only available in a single strength, which does not need to be indicated on a prescription. These differences would decrease the potential risk of medication errors occurring between these two products.

Writing Sample:



Zymar *Zyvox*

DMETS had look-alike concerns between the proprietary names *Zymine* and "Zymar". *Zymine* contains triprolidine hydrochloride and is indicated for the symptomatic relief of perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis caused by inhalant allergens and foods, and mild uncomplicated allergic skin manifestations of urticaria and angioedema. Both proprietary names share the same beginning "Zym". The "ine" in *Zymine* and "ar" in "Zymar" may look similar when scripted (see below). Even though both drug products are available in one strength and are both in liquid form, they have different routes of administration (oral vs. ophthalmic), and different directions of use (One drop every 2 hours in the affected eye(s) while awake, up to 8 times daily, on days 1 and 2, and instill one drop up to 4 times daily while awake on days 3 through 5 vs. 10 mL every 4 to 6 hours). Since the directions of use for "Zymar" are cumbersome, they would likely be written out on a prescription or written as "use as directed". According to data provided by [redacted]
The [redacted] sales of *Zymine* along with the differences in the products would help decrease the potential risk of medication errors occurring between these two drug products.

Writing Sample:

Zymine *Zymar*

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

The carton labeling and container labels were submitted in draft text formats that did not allow for a complete review. However, DMETS reviewed the submitted draft labeling, package insert, and labels and identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (0.3%: [redacted], 2.5 mL, and 5 mL)

The strength, 0.3%, on the front panel should be made more prominent by, for example, bolding "0.3%".

B. CARTON LABELING (0.3%: [redacted], 2.5 mL, and 5 mL)

See above CONTAINER LABEL comment.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name "Zymar".

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 and established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name "Zymar" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Jennifer Fan
2/21/03 09:50:34 AM
PHARMACIST

Denise Toyer
2/21/03 12:52:10 PM
PHARMACIST

Carol Holquist
2/21/03 03:28:18 PM
PHARMACIST

Jerry Phillips
2/21/03 04:15:05 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 24

Bruce I. Bodner, M.D.
Virginia Eye Consultants
403 Medical Tower
Norfolk, Virginia 23507

Dear Dr. Bodner:

On September 9-13, 2002, Mr. Stephen Eason, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #SPCL-GFLX 3/02 entitled: "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Acute Bacterial Conjunctivitis") of the investigational drug gatifloxacin ophthalmic solution, performed for Allergan. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of the research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. Eason presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not adhere to the approved protocol (21 CFR 312.60).

1. Conjunctival swabs for bacterial culture were not obtained within the protocol specified interval for subjects 2333 (visit 2), 2240 (visit 2), and 2471 (visit 3).

2. The protocol states, "At no time is an entry to be made in the diary by anyone other than the subject or the subject's legal guardian." Your study staff completed portions (dates) of subject diaries for 14 subjects.

Please make appropriate corrections/changes in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Eason during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Tomas Coronado, M.D.
730 North Main Street
Suite 719
San Antonio, Texas 78205

NOV 29

Dear Dr. Coronado:

On September 3-6, 2002, Ms. Iris Macinnes, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical investigation (protocol #SPCL-GFLX 3/02 entitled: "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Acute Bacterial Conjunctivitis") of the investigational drug gatifloxacin ophthalmic solution, performed for Allergan. 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 ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator MacInnes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV - 4

Michael Tepedino, M.D.
Cornerstone Eye Care
307 N. Lindsay Street
High Point, North Carolina 27262

Dear Dr. Tepedino:

This letter informs you that you did adhere to the Food and Drug Administration (FDA) regulations governing the conduct of clinical investigations and the protection of human subjects.

Between September 3 and September 5, 2002, Ms. Eileen J. Bannerman, from FDA, met with you to review your conduct of clinical studies (protocol #SPCL-GFLX 3/01, "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of Placebo in the Treatment of Acute Bacterial Conjunctivitis" and #SPLC-GFXL 3/02, "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Acute Bacterial Conjunctivitis") of the investigational drug ——— (gatifloxacin ophthalmic solution 0.3%), performed for Senju Pharmaceutical Co., Ltd. This inspection, as part of FDA's Bioresearch Monitoring Program, is designed to validate clinical studies on which drug approval may be based and to ensure the protection of the rights and welfare of human research subjects.

We appreciate the cooperation shown Investigator Bannerman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely yours,

/S/

for Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc: Beverly A. Karasick, Director of Compliance

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 2 3 ...

Monica L. Monica, M.D., Ph.D.
Lakeview Vision
143 Robert E. Lee Boulevard
New Orleans, Louisiana 70124

Dear Dr. Monica:

This letter informs you that you did adhere to the Food and Drug Administration (FDA) regulations governing the conduct of clinical investigations and the protection of human subjects.

Between August 20 and 28, 2002, Ms. Donna Gallien, from FDA, met with you to review your conduct of a clinical study (protocol #SPCL-GFLX 3/01 entitled: "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of Placebo in the Treatment of Acute Bacterial Conjunctivitis") of the investigational drug gatifloxacin ophthalmic solution, performed for Allergan. This inspection, as part of FDA's Bioresearch Monitoring Program, is designed to validate clinical studies on which drug approval may be based and to ensure the protection of the rights and welfare of human research subjects.

We evaluated the inspection report and the documents submitted with that report and agree with Ms. Gallien's conclusion.

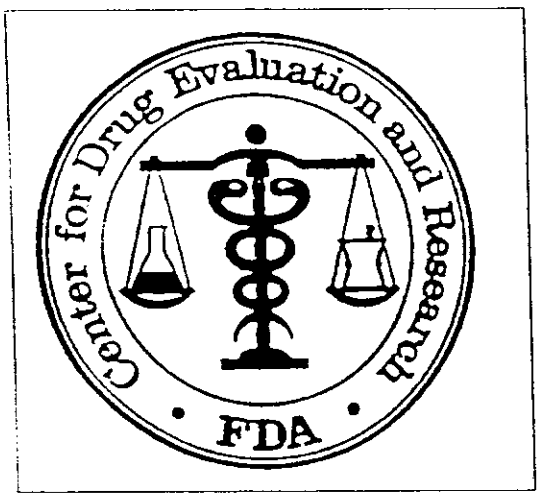
We appreciate the cooperation shown Investigator Gallien during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FACSIMILE TRANSMISSION
RECORD



From: Libaniel Rodriguez.
Review Chemist

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

Phone 301-827-2069
Fax 301-827-2531

Date: August 30, 2002

To: Name: Elizabeth Bancroft
Company: Allergan,Inc.
City: Irvine State:CA
Phone #: 714 246 4391

FAX #: 714 246 4272

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2069MMEDIATELY if re-transmission is necessary.

If you have any question about this information request, please call me.

Libaniel Rodriguez

August 30, 2002

NDA 21-493 — (gatifloxacin ophthalmic solution) 0.3%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

DRUG PRODUCT

1. Please submit stability data and HPLC chromatograms for registration lot 11902, sublots C3, C4, C5, C6 and D, at room temperature and accelerated conditions.
2. Please submit stability data at 30°C/60%RH for all the sublots of the three registration stability lots.
3. Please submit all the available stability data for the commercial-scale batches 15499, 15507 and 15599 manufactured in Waco, Texas, and for batches E21182, E21166 and E21171 manufactured in Westport, Ireland.
4. Please submit three methods validation packages.

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/s/

Libaniel Rodriguez
8/30/02 10:05:02 AM
CHEMIST
IR#1

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Elizabeth Bancroft, Allergan	**From:** Lori Gorski, Project Manager
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone: 714-246-4391	**Phone:** 301-827-2521
Pages: 1 including cover sheet	**Date:** August 26, 2002

Re: Gaifloxacin clinical reviewer request for clarification- NDA 21-493

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:** Elizabeth,

For study 3/01

There was a statistically significant difference (0.034) found in the treatment-by-investigator analysis for the per protocol population (N=100). This was addressed by defining a new per protocol population (N=106) and re-running the analysis which found the p-value to be 0.167. Please provide the division with the rationale for adding the additional 6 patients to the per-protocol population and if this population is to be used, the efficacy and safety data throughout the submission needs to be corrected reflecting this change. Alternatively, a sensitivity analysis on the original population (n=100) should be performed to identify which investigator site is skewing the outcome.

In addition, perform the treatment-by-investigator and treatment-by-group analysis for the mITT group as was done in study 3/02.

Please provide a response with an amendment to the NDA.

Call me if you have any questions. Thanks, Lori

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/s/

Lori Gorski
8/26/02 01:36:44 PM
CSO

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MEETING MINUTES

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

MEETING DATE: November 26, 2001 **TIME:** 2:30 PM EST

Pre-NDA: [redacted]
DRUG: Gatifloxacin ophthalmic solution 0.3%

Meeting Request Submission Date: October 15, 2001
Date Sponsor Requested: November 26, 2001
Briefing Document Submission Date: November 2, 2001

SPONSOR/APPLICANT: Allergan

MEETING TYPE: Pre-NDA meeting - application due in March 2002.

FDA PARTICIPANTS:
Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
Bill Boyd, Medical Officer
Jennifer Harris, Medical Officer
Lisa Hubbard, Clinical Reviewer
Raphael Rodriguez, Project Manager
Shawn Kheirshidi, Chemist
Linda Ng, Chemistry Team Leader
Zhou Chen, Pharm/Tox Reviewer
Laura Lu, Statistical Reviewer
Carmen DeBellas, Supervisory CSO
Jonca Bull, Acting Office Director, ODE5

INDUSTRY PARTICIPANTS:
Tom Carpenter, Toxicology
Dave Garbe, Medical Communication (Labeling)
Richard Graham, Chemistry
Harold Jensen, Clinical Micro / Clinical Research
Peter Kresel, Regulatory Affairs
Julie Mordaunt, Biostatistics
Scott Whitcup, Clinical Research
Rhett Schiffman, Clinical Research
Josephine Cheng, Reg Affairs
Satoshi Ishiwawa, Kyorin Pharmaceutical Co., Ltd

MEETING OBJECTIVES: To gain additional guidance in preparation of the NDA submission for March 2002.

BACKGROUND INFORMATION: Gatifloxacin solution is intended to treat bacterial conjunctivitis. It is a fluroquinolone anti-baterial agent developed by Kyorin Pharmaceuticals Ltd. (Tokyo, Japan) as tablets NDA 21-061 Tequin and IV NDA 21-062. The ophthalmic formulation was developed by [redacted]

DISCUSSION ITEMS:

OVERALL

1. Allergan intends to submit the NDA in electronic format in compliance with the FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format – NDAs". Does FDA want a paper copy of any or all parts of the NDA?

   Response: ***Although paper copies are not formally requested, desk copies of relevant sections of the NDA would greatly speed the reviewer's work.***

   Any electronic files available in Word (submitted as desk copies) would also speed the review process.

CHEMISTRY

1. The API specification for water content set by the manufacturer is [redacted] Allergan proposes [redacted] No impact on API quality or stability is expected. The API is added to the finished product by assay value, so there is no impact on the finished product.

   Batches recently received by Allergan have [redacted] during the processing of the API. The precision of the USP Karl Fisher method for water determination is not considered sufficient to reliably differentiate small differences in water content. Therefore, a batch reported as containing [redacted] water by the manufacturer might easily yield a value at or slightly higher than the [redacted] upper specification upon retest by Allergan. The [redacted] for the upper specification will allow for reasonable method variability in water measurements of API containing water near [redacted] Does the Agency agree with the proposed specification?

   Response: This is a review issue that will be addressed in the review of the NDA. The Agency will comment on any proposal for water content acceptance criterion when all relevant data to justify the proposal are submitted.

PRECLINICAL

1. There are no preclinical concerns for this NDA.

MICROBIOLOGY

1. Preservative Efficacy data, Sterility Test validation data, and Aseptic Process Validation data will be included in the Microbiology Section. Please confirm this is acceptable.

   Response: Acceptable.

Additional Comments from the Reviewer

1. The "*in vitro* susceptiblity listing of organisms is still part of labeling at the present time. Data from the original NDA can be used (if a letter of authorization is submitted). Any organisms in gatifloxacin's label that are associated with conjunctivitis may be placed in the label (in the *in vitro* susceptibility listing).

2. If additional organisms are proposed for the label, at least 100 isolates should be tested in at least two different studies by different investigators. The MIC90 values in these studies must be below the susceptible breakpoint indicated in the gatifloxacin label. The organisms must also be associated with bacterial conjunctivitis.

3. A table should be included in the NDA submission that list each pathogen from the clinical trials and its eradication rate by MIC value.

CLINICAL/BIOSTATISTICS

1. It is our understanding that during the end of phase 2 meeting between the Agency, Senju (the original Sponsor of the IND) and [redacted] representing Senju), the Agency indicated that Senju did not need to do additional *in vitro* susceptibility testing on bacterial isolates other than those obtained during the phase 3 studies. Allergan is not aware of any decisions that have been made by the Agency to not allow the "*in vitro* susceptibility" section into the product labeling for conjunctivitis. It is felt that without this additional *in vitro* data we would be at a disadvantage with competing topical antiinfective products.

   Allergan would like to submit *in vitro* data from ocular bacterial isolates indicating the *in vitro* efficacy for important ocular pathogens not isolated during the phase 3 conjunctivitis studies, and to include this information in the package insert. If this is acceptable, how many susceptible isolates for each strain need to be documented?

   Response: Senju asked if there was a need to do additional in vitro *susceptibility testing of bacterial isolates obtained from the eyes of culture positive patients during the clinical studies, the agency response was "No."*

   It would be acceptable to submit in vitro *data from ocular bacterial isolates indicating the* in vitro *efficacy for important ocular pathogens not isolated during the phase 3 conjunctivitis studies.*

   Micro: *There is a proposed Federal Register rule that indicated that this section may be eliminated but it has not been finalized. This section is part of labeling at the present time. Data from the original NDA can be used (if a letter of authorization is submitted). Any organisms in gatifloxacin's label that are associated with conjunctivitis may be placed in the label.*

   If additional organisms are proposed at least 100 isolates should be tested in at least two different studies by different investigators. The MIC_{90} values in these studies must be below the susceptible breakpoint indicated in the gatifloxacin label. The organisms must also be associated with bacterial conjunctivitis.

2. After Allergan took over the management of the phase 3 clinical studies, we found that all Investigators were instructed to list conjunctivitis as an adverse event if the contra-lateral eye developed conjunctivitis, or if the "treated eye" with conjunctivitis worsened. We believe that conjunctivitis in the contra-lateral eye is the normal progression of unilateral conjunctivitis and that if conjunctivitis worsened during treatment, that this would indicate treatment failure and not an adverse event.

2a. Allergan does not consider these cases of conjunctivitis as adverse events caused by a treatment of conjunctivitis and would not expect this in the product labeling. Does the Agency agree?

   Response: Agree.

2b. Because these data were collected as adverse events they will be presented as adverse events in an in-text table with an explanation of the way the adverse events were reported. Is this acceptable?

Response: Agree

3. Included within this background package is the Statistical Analysis Plan for the Integrated Summaries of safety and efficacy. This document describes the analysis plan of the integrated summaries of safety and efficacy for the clinical study data of the two double-masked clinical studies, SPCL-GFLX 3/01 and SPCL-GFLX 3/02. Included are the hypotheses of interest, the statistical methods to be used, and the format of the tables to be produced. Does the Agency accept the plans as specified in this document?

Response: The agency would like to see two analyses for each protocol: an intent to treat (with last observation carried forward) analysis, and a per protocol (observed cases only analysis).

[Allergan clarified that an intent to treat analysis is planned for each individual phase 3 study. Additional analyses may be submitted in the NDA, but the ITT and PP analyses would provide the primary basis for approval.]

4. Allergan proposes [redacted]

Response: It would be preferable to have these datasets also submitted as Excel spreadsheets.

Lori Gorski
Project Manager

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

MEETING MINUTES

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/s

Lori Gorski
6/14/02 09:53:56 AM
Lori Gorski has signed for Carmen Debellas

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-493

Allergan, Inc.
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Ms. Bancroft:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [redacted] (gatifloxacin ophthalmic solution 0.3%)

Review Priority Classification: Standard (S)

Date of Application: May 29, 2002

Date of Receipt: May 30, 2002

Our Reference Number: NDA 21-493

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 29, 2002, in accordance with 21 CFR 314.101(a).

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov cder pediatric) for details. We acknowledge your request for deferment of your pediatric studies until December 2004. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-493	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zymar (gatifloxacin ophthalmic solution 0.3%)		Applicant: Allergan, Inc.	
RPM: Lori M. Gorski		HFD-550	Phone # 301-827-2090
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

✣ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3 – New Dosage Form
• Other (e.g., orphan, OTC)	
✣ User Fee Goal Dates	March 30, 2003
✣ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
✣ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
✣ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
✣ 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.	(X) Verified
✣ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (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).	(X) Verified
✣ Exclusivity Summary (approvals only)	March 28, 2003
✣ 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)	none
• 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) None ( ) 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	Clinical review of March 27, 2003
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC – March 14, 2003 ODS February 21, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	None
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	See review of March 27, 2003
• Applicant proposed	March 25, 2003
• Reviews	March 27, 2003
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	None
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	November 26, 2001
• Pre-Approval Safety Conference (indicate date; NME approvals only)	Not required
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	None
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	None

Clinical/Clin. Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	None
❖ Clinical review(s) *(indicate date for each review)*	March 3, 2003, December 5, 2002 (SU), February 13, 2003, March 25, 2003, March 27, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	Clinical – September 23, 2002
❖ Safety Update review(s)	See above
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	March 28, 2003
❖ Statistical review(s) *(indicate date for each review)*	January 8, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	August 1, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See package
• Bioequivalence studies	None

CMC Information	
❖ CMC review(s) *(indicate date for each review)*	March 7, 2003, March 19, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	In CMC review
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s)	Sterility – August 12, 2002
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) 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)*	January 22, 2003
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	None
❖ CAC/ECAC report	None

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/s/

Lori Gorski
3/28/03 02:57:00 PM

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