CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-670/S-015

50-693/S003

50-730/S005

CORRESPONDENCE

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
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N50-711

Central Research

January 13, 2000

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW. FURTHER DISSEMINATION MAY ONLY BE MADE WITH THE EXPRESS WRITTEN PERMISSION OF PFIZER INC.

ATT: DOCUMENT CONTROL ROOM
12229 Wilkins Ave.
Rockville, MD 20852

Copy to: Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

ATT: DOCUMENT CONTROL ROOM
12229 Wilkins Ave.
Rockville, MD 20852

Dear Doctor Goldberger and Doctor Chikami:

Re: NDA-50-730 - ZITHROMAX® (CP-62,993, azithromycin) - MAC OPPORTUNISTIC INFECTIONS
NDA-50-670* - ZITHROMAX® (CP-62,993, azithromycin) Capsules
NDA-50-693* - ZITHROMAX® (CP-62,993, azithromycin) - Oral Suspension

Pursuant to Paragraph 505(b) of the Federal Food, Drug and Cosmetic Act, and 21 CFR, Part 314.70(b)(3), and subject to the exemption provisions contained in Section 125(d)(2) of Title I of the FDA Modernization Act of 1997, we are submitting a Supplemental New Drug Application (sNDA) to the Division of Special Pathogens and Immunologic Drug Products (HFD-590) for the use of Zithromax 600 mg tablets, in combination with ethambutol, for the treatment of disseminated *Mycobacterium avium Complex* (MAC) in patients with AIDS. In addition, we are seeking an indication for the same dosage to be used in combination with other anti-mycobacterial agents to treat pulmonary MAC infections in non-HIV infected patients.

This Application consists of 55 uniquely numbered paper volumes. The electronic archive consists of one electronic tape organized according to the archive Table of Contents provided in the electronic submission. **Attachments I and II** to this letter contain additional content-specific information.

Reference is made to Pfizer's New Drug Application, NDA-50-730, approved June 12, 1996, for the use of Zithromax 600 mg tablets in the prevention of disseminated *Mycobacterium avium Complex* (MAC) infection in patients with advanced AIDS. Reference is also made to two other New Drug Applications: NDA-50-670, the original Zithromax Capsules NDA, approved November 1, 1991, and NDA-50-693,

Zithromax Oral-Suspension, approved September 28, 1994. These latter two applications are under the jurisdiction of the Division of Anti-Infective Drug Products (HFD-520). As labeling for the 600 mg tablets also covers the latter two products, this letter and copies of the proposed labeling are being submitted to these NDAs for cross-reference. To facilitate your review of previously approved Zithromax product labeling, we have included the text from all three approved ZITHROMAX package inserts in Section 3.A.2 of this Application.

We specifically refer to:

- NDA-50-670 (250 mg capsules, approved November 1, 1991) for information on drug substance Chemistry, Manufacturing and Controls, animal pharmacology and toxicology, and clinical pharmacology,
- NDA-50-711 (approved July 18, 1996) for the Chemistry, Manufacturing and Controls for the 250 mg tablets, which were used in some of the clinical studies,
- NDA-50-730 (600 mg tablet, approved June 12, 1996), the parent Application for this Supplement, for drug product Chemistry, Manufacturing and Controls, pharmacokinetics (including absolute bioavailability) and background information on the microbiology of *M. avium* Complex.
- NDA-50-733 (500 mg vials for intravenous infusion, approved January 30, 1997) for Human Pharmacokinetics and Bioavailability, regarding pharmacokinetic data relating to intravenous administration.

Summary:

This supplemental New Drug Application contains data supporting the daily use of 600 mg Zithromax tablets administered in combination with ethambutol for the treatment of *Mycobacterium avium* Complex (MAC) in AIDS patients. Clinical studies supporting the efficacy, safety and favorable pharmacokinetic profile of this treatment regimen are included in this sNDA. The results obtained with this treatment regimen are comparable to that of clarithromycin given 500 mg b.i.d. in combination with ethambutol. Our submission also contains data supporting an indication for the treatment of pulmonary MAC infections in non-HIV infected patients using Zithromax 600 mg daily in combination with other anti-mycobacterial agents. This latter indication is based primarily on the publications of Dr. Richard Wallace, University of Texas, all of which have been provided in this sNDA. Our review of Dr. Wallace's data confirms the conclusions regarding efficacy and safety reported in his publications. Pulmonary MAC is an indication for which there are no approved therapies. Consequently, with the efficacy of Zithromax as presented in this Application, we are prepared to support the Agency should it consider a Priority Review of this Application.

Clinical Efficacy Data

Studies using Zithromax 600 mg tablets in the treatment and prevention of MAC, as well as related clinical pharmacology studies, were conducted under [redacted]

Data from a single pivotal, multicenter Phase III study (Study #066-189), and five other Pfizer-sponsored studies (Study #066-148, 066-131, 066-169, 066-162/162X/148B and 066-354/354A), are provided in Section 8 of this Application to support the safe and effective use of Zithromax in the treatment of disseminated MAC infection in severely immunocompromised, HIV-infected patients. For completeness, we have also included a report in the Clinical Publications section from a study in MAC treatment conducted by the Veterans Affairs Research Consortium (Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Clin Infect Dis 1998;27:1278-85). In addition, we have enclosed a collection of publications and microbiologic results of clinical trials conducted by Dr. Richard Wallace (University of Texas) on the use of Zithromax 600 mg/day in the treatment of pulmonary MAC infections in

non-HIV patients. Supporting data generated from Pfizer's analysis of data from Dr. Wallace's center has also been included. Authorization for the Agency to refer to Dr. Wallace's regulatory documents has been forwarded to the Division. A copy of his Letter of Authorization is enclosed as **Attachment III** to this cover letter (see below).

Pivotal study #066-189 compared the use of azithromycin 600 mg/day versus clarithromycin 500 mg b.i.d. Both treatment arms employed combination therapy with 800 or 1200 mg daily doses of ethambutol. Upon enrollment, patients with disseminated MAC disease received therapy and were monitored for up to 24 weeks (to achievement of sterility of their blood cultures). The primary endpoint for the analysis was the percentage of patients achieving clearance of MAC from the blood at Week 24. Other endpoints include the following: the durability of the response (duration of negative culture following achievement of sterility), percentage of patients achieving sterility at any time point, resolution of symptoms associated with disseminated MAC disease, correlation of clinical response with microbiological response, and survival. [Note that the third arm of this study, 250 mg azithromycin/day plus ethambutol, was dropped after a blinded interim analysis indicated that this dosage was less effective with respect to achievement of sterility at 12 weeks. In July 1996, Pfizer informed the Division of this decision.] The data from all randomized subjects (n = 246) are included in the study report (Table 1.1). There were 91 patients randomized to azithromycin 600 mg/day, 90 patients randomized to clarithromycin 500 mg b.i.d., and 65 patients randomized to azithromycin 250 mg/day.

Pharmacokinetics
Section 6 (Human Pharmacokinetics and Bioavailability) contains data from 90 subjects, including 75 exposed to azithromycin, 26 receiving placebo, and 46 receiving comparative agents (subjects may have been crossed over to more than one treatment).

The pharmacokinetics of multiple daily doses of 600 mg of Zithromax are reported in a single Phase I trial, Study #066-077. In addition, we are providing the results of four interaction studies of azithromycin with the following therapies expected to be used with azithromycin by AIDS patients: indinavir (Study #066-085), fluconazole (Study #066-086), trimethoprim-sulfamethoxazole (Study #066-088) and nelfinavir (Study #066-094). These study reports were previously submitted to [redacted] Except for the nelfinavir study, Study 066-094, none of the other interaction studies demonstrated a significant drug interaction with azithromycin. A single 1200 mg dose of azithromycin, when administered with nelfinavir at steady state, produced a 16% decrease in the AUC of nelfinavir and its M8 metabolite. In addition, nelfinavir at steady state was associated with a 113% increase in AUC and a 136% increase in mean Cmax of azithromycin when administered as a 1200 mg dose. The results from this interaction study were initially communicated to Division Reviewers in a teleconference on June 21, 1999, and a copy of the final Phase I study report was submitted to the IND the same day (serial number 227).

Included in the Appendix I to Section 6.A is the Package Insert for SUSTIVA® efavirenz (Dupont), in which no significant interaction with azithromycin was observed. We have included this result in our proposed labeling for this supplement (see section on Labeling below).

Safety
We have included the results of several studies performed in AIDS patients for conditions other than MAC (Non-MAC Studies) that support the safety of ZITHROMAX given as daily doses similar to the proposed 600 mg regimen over extended periods of time.

The MAC treatment studies contain safety data from a total of 716 patients. The non-MAC studies describe safety results on the treatment of 923 patients. In addition, 15 subjects received azithromycin in 5 miscellaneous and terminated studies of azithromycin in opportunistic infections. In all, 1568 patients with opportunistic infections, not including patients treated by Dr. Wallace or other independent

investigators, have been treated with azithromycin (including some given intravenous azithromycin) in Pfizer-sponsored Phase II/III studies using repeated daily dosages. In addition, 146 patients have been treated with comparators (n=86) or placebo (n=60). Some patients could be treated with more than one regimen.

On February 7, 1999, the Division notified Pfizer that in addition to the inclusion of listings of Spontaneously Reported Serious Adverse Events, it was requested that an assessment be made of overall safety in patients treated since the MAC prophylaxis approval. On March 2, 1999, Pfizer agreed to examine Serious Adverse Events (SAEs) in spontaneous reports from the approval date for MAC (June 12, 1996) forward. The reports for Spontaneous SAEs and the relevant discussion are contained in Appendix IV of Clinical Data Section 8. This information is reported in two parts: Part 1 contains SAEs and discussion to a cutoff date of July 26, 1999. Since the safety cutoff for our project database was extended to November 22, 1999, we have included an incremental listing from July 27 to November 26, 1999 (Part 2).

Microbiology
Section 7 (Microbiology) contains an updated review of the literature relating to MAC, as per the request from Ms. Linda Gosey, Microbiology Reviewer, at the Pre-NDA teleconference, December 21, 1998. In addition, Section 7 contains a summary of the clinical microbiology data obtained from pivotal study 066-189. [Note that susceptibility testing of breakthrough isolates from the open-label extension (Study 066-189B) is still in progress. We will provide information on these isolates during the review of the Application.]

Labeling
We have included a statement in the DOSAGE AND ADMINISTRATION section proposed labeling that in the event that oral administration is not feasible, patients may receive ZITHROMAX I.V. at a daily dose of 250 mg. At our September 8, 1999 teleconference with the Division, Pfizer was requested to justify the use of this intravenous dose based on pharmacokinetic information. In the CLINICAL PHARMACOLOGY section of the approved labeling, we reference the absolute bioavailability of two 600 mg tablets as 34%, based on the results from Phase I study 066-062, submitted in the original MAC prophylaxis NDA. We believe that this justifies the use of this intravenous dose. Pfizer will provide further documentation for this rationale prior to the 60-day filing deadline for the sNDA.

We have included the results of an interaction study with efavirenz, conducted by Dupont, in our proposed labeling for this supplement. A Letter of Authorization from Dupont is included as **Attachment IV** (see below).

Marketing Status
At present, ZITHROMAX is not marketed for the treatment of disseminated MAC disease in any country. Countries with approval for prevention of disseminated MAC in AIDS patients are listed in Appendix I of the Application Summary (Section 3) and Clinical Section (Section 8).

Safety Update – Submission Status
We note that based on discussions with the Division regarding the timing of this Application, all relevant data for the cohort of patients being studied has been collected and included herein. Therefore, in a teleconference on September 8, 1999, Pfizer and FDA agreed that a Four-Month Safety Update would not be necessary. We will gladly provide an additional correspondence letter to the NDA file at the requisite time if such an administrative step is required.

Pediatric Final Rule
We acknowledge a discussion with the Division on September 8, 1999, regarding compliance with requirements of the Pediatric Final Rule. Included in this Application are all available data from pediatric subjects treated compassionately with azithromycin for various opportunistic infections. We do not believe there is sufficient information to support a claim for the treatment of MAC in children, nor is it likely that such a study could ever be conducted in the foreseeable future, given the very low incidence of disseminated MAC in children. We will, however, attempt to extrapolate suitable dosing recommendations based on pharmacokinetic information from short-term treatment in non-HIV infected children and HIV-positive and HIV-negative adults. These conclusions will be provided as a response to a Division query during the review of the Application, as an NDA amendment, prior to the 60-day filing deadline. Based on the advice of the Division from the September 8 teleconference, we will await the review of our pediatric data and further guidance with respect to the issue of a request for a waiver from conducting pediatric studies in the treatment of disseminated MAC.

Submission Requirements
In accordance with the requirement of the Generic Drug Enforcement Act of 1992, and in connection with this Application, Pfizer Inc did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

Pursuant to the Prescription Drug User Fee Act of 1992, the applicable user fee for this submission has been remitted for a Supplemental NDA with Clinical Data to NDA-50-730. The User Fee ID number for this Supplement is 3672. Copies of this user fee cover sheet have been included in the copies of this cover letter being submitted to NDA's 50-670 and 50-693.

Pursuant to 21 CFR 314.54(a)(4), Pfizer has prepared a field copy of Sections 1-4 of this Application to be forwarded to Ms. Brenda Holman, Director, New York District Office, 158-15 Liberty Avenue, Jamaica, NY 11433. This is a true copy of the relevant technical sections under 21 CFR 314.50(k)(3) in the archival and review copies of this Application. We note a teleconference with Mr. Jerry Woyschner, Director, Investigations, for the NY District Office on January 5, 2000, during which Pfizer was advised to delay shipment of this field copy until February 1, 2000, since the office was in the process of relocating from Brooklyn to the Queens address. Ms. Laurie Bernato, Regulatory Project Manager, was informed of this procedural modification on January 5, 2000.

Financial Disclosure
As discussed in a teleconference with the Division on September 8, 1999, we are providing in Section 19 of this Application information relating to Financial Disclosure by Clinical Investigators to the extent of Payments of Other Sorts for covered study 066-189 from February 2, 1999 until a cutoff of July 30, 1999. Pfizer will continue to collect and internally retain information on Payments of Other Sorts for this study through the one year anniversary of the September 16, 1998 close of the trial (July 31 through approximately September 16, 1999).

Description of Attachments to this Cover Letter
Please refer to **Attachment I** of this cover letter for additional information relevant to the content of this Application. Please refer to **Attachment II** of this cover letter for a guide to the review of this Application.

Attachment II also describes the degree to which this Application will adhere to the Guidance for Providing the Archive in Electronic Format. Reference is made to our Pre-NDA teleconference of December 21, 1998 and follow-up teleconference of September 8, 1999, regarding Pfizer's intention to provide a fully electronic submission, in addition to the paper archival copy. Case report forms and case report tabulations are provided in electronic format only. Regarding electronic data, we are providing data sets for Study 066-189 as SAS transport files in the review aid and archive. Raw pharmacokinetic data for the five studies included in this application has been provided as CSV files in the review aid, in addition to

SAS transport files in the archive. Tabulated results from the pulmonary MAC studies of Dr. Richard Wallace are provided electronically as SAS transport files in the review aid and archive. We have also agreed to provide technical support to your Reviewers upon request, as well as directed training shortly after the Division receives the application.

Attachment III contains a Letter of Authorization from Dr. Richard Wallace, University of Texas, permitting Pfizer to cross-reference his IND [redacted] for additional information of the use of azithromycin in Pulmonary MAC.

Attachment IV contains a Letter of Authorization from Dupont Pharmaceuticals, allowing for the cross-reference to the NDA-20-972 for SUSTIVA® efavirenz.

We have replaced Subsection 3.H.2.B (Overview of Clinical Studies, Interactions with FDA), from the Application Summary Volume, with a placeholder statement and provided the subsection as **Attachment V** to this cover letter.

Per prior discussions with members of your Project Management staff, we are forwarding various desk copies of sections of this Application to Ms. Bernato, Regulatory Project Manager, HFD-590, for further distribution to Reviewers. A desk copy of this cover letter is being forwarded to Mr. Jose Cintron, Regulatory Project Manager, HFD-520.

Following receipt of this Application by the Division, Pfizer will install the electronic review aid on the Division's network server and will provide additional Netscape WEB-browsing software to Reviewers who request it. We note that Pfizer and CDER now have capabilities for sending and receiving encrypted electronic mail between any two users, thereby obviating the need to establish point-to-point contact.

If you have any questions regarding this correspondence, please contact Dr. Ronald Trust of our Groton, Connecticut office, at (860) 441-6991 (phone), (860) 441-0870 (FAX) or ronald_i_trust@groton.pfizer.com (electronic mail). Please include this information in our files for NDA-50-730, NDA-50-670, and NDA-50-693.

Sincerely yours,

Steven W. Ryder, M.D.
Senior Vice President
U.S. Clinical Research

Ronald I. Trust, Ph.D., MBA
Associate Director II
Regulatory Affairs Department

Desk Copies: Jose Citron (cover letter & attachments)
Laurie Bernato (3 desk copies of phase II-III study reports, 5 desk copies of ASV)

RIT/rmh
Attachments
*(volume 1 only)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Drfile
50-730

Food and Drug Administration
Rockville MD 20857

NDA 50-730/S-005, S-006 **PRIOR APPROVAL SUPPLEMENT**

Pfizer, Inc.
Attention: Ronald I. Trust, Ph.D., MBA
Associate Director II
Regulatory Affairs Department
Eastern Point Road
Groton, CT 06340

MAR 9 2000

Dear Dr. Trust:

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

Name of Drug Product: Zithromax ® (azithromycin tablets) 600 mg

NDA Number: 50-730

Supplement Numbers: S-005, S-006

Therapeutic Classification: Standard (S)

Date of Supplement: January 13, 2000

Date of Receipt: January 13, 2000

These supplements propose the following changes:

1. Use of Zithromax ® 600 mg tablets, in combination with ethambutol, for the treatment of disseminated Mycobacterium avium Complex (MAC) in patients with AIDS

2. Use of Zithromax ® 600 mg tablets in combination with other anti-mycobacterial agents to treat pulmonary MAC infection in non-HIV infected patients

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 March 13, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 13, 2000 and the secondary user fee goal date will be January 13, 2001.

pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirement 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 120 days of 8/receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

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 notify you within 120 days of receipt of your response whether a waiver is granted. 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. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. 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 application numbers listed above at the top of the first page of any communications concerning this application. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Laurie Bernato, R.N., MN, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen
and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research