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APPLICATION NUMBER:

50-670/S-015

50-693/S003

50-730/S005

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	050730	**Trade Name:**	ZITHROMAX (AZITHROMYCIN)
Supplement Number:	005	**Generic Name:**	AZITHROMYCIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	AZALIDE ANTIBIOTIC
Action Date:	11/13/00		

Indication # 1 Use of Zithromax Tablets, 600 mg, in combination with ethambutol, for the treatment of disseminated Mycobacterium avium complex (MAC) infections in persons with advanced HIV infection

Label Adequacy: Other - See Comments

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	5/13/02

Comments: Division has agreed to work with sponsor on establishing data needed to satisfy Pediatric Rule (sponsor may already have these data in-house) as well as wording for the labeling

This page was last edited on 1/18/01

/S/ January 18, 2001

Signature Date

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: March 3, 2000

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

ADDRESS: Pfizer Inc.
Eastern Point Road
Groton, CT 06340
Telephone: (860) 441-6991
FAX: (860) 441-0870

FROM: D. Laurie Bernato
Regulatory Project Manager

NDA: 50-730/S-005, S-006

DRUG: Zithromax ® (Azithromycin)

SUBJECT: Supplement Classifications

FDA Attendees, Titles and Offices:

Marc Cavaillé-Coll, MD Ph.D., Medical Team Leader
Thomas Hassall, MS, Assistant Dir. For Regulatory Affairs ODE IV
D. Laurie Bernato, RN, MN, Regulatory Project Manager
Ellen C. Frank, R.Ph., Chief, Project Management Staff
Diana Willard, Regulatory Project Manager

Pfizer Attendees, Titles and Officers:

Ronald Trust, Ph.D., MBA, Regulatory Strategy and Registration
Rebecca Benner, Ph.D., Biometrics
Michael Dunne, MD Clinical Systems
James Kenney , Ph.D., Project Management
Laurel Davis, MD Clinical Systems
Philip Ross, MD Clinical Systems

Meeting Objective:

The purpose of the teleconference was to inform Pfizer that their submission, dated January 13,2000, would be classified as two supplements.

Background:

Pfizer submitted a supplemental NDA on January 13, 2000. It proposed adding two new indications to the label:

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 infections in non-HIV infected patients.

An internal meeting was held February 28, 2000 to discuss whether this should be reviewed as one supplement or two.

Discussion:

The Division advised Pfizer that they had determined that the proposed change was two separate indications and would be reviewed as two efficacy supplements. The Division noted that the same data was required to review each of the two indications. Therefore, in administratively splitting this into two supplements, we would be consider that all the data was contained in one supplement for which Pfizer would pay a user fee. The second supplement would refer to the first supplement and would not require a user fee.

Pfizer inquired whether the review was positive. The Division responded that it was too early to determine this.

Action:

The Division advised Pfizer that they did not need to send any additional correspondence regarding this administrative split. The acknowledgement letter to be sent by the Division and the minutes of this teleconference would serve as record of the split.

NDA 50-730/S-005
S-006

HFD-590
D. Willard

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: April 6, 2000

TO: Ronald Trust, Ph..D., MBA

ADDRESS: Pfizer Central Research

TELEPHONE: 860-441-6991

FAX: 860-441-0870

FROM: Diana Willard

APPLICATION: NDA 50-730

SUBJECT: Microbiology Issues for April 14, 2000 teleconference

Microbiology questions:

1. Were clarithromycin MICs determined on the MAC isolates obtained from clinical protocols [redacted] What susceptibility testing method has used to determine these MIC values?

2. In study 189 did you conduct ethambutol susceptibility testing against the MAC isolates?

3. In the data files individual azithromycin and clarithromycin MICs were expressed (i.e. MIC 6.7, 9.4 ug/ml). How did you convert these individual MICs into the MIC categories described in the various tables found in volume 11 pages 9-16.

4. Please provide the following MICs on the MAC isolates recovered at the following time points:

Study 189

Patient #	Time point
31A0053	week 9
31A255	month 18 and 19 in study 189B
32A0015	week 6
42B006	week 9
42B0090	week 12
42B0175	week 20
42E120	week 9
54E0026	week 16

54E0079	week 12
54E0083	week 20
54E0228	week 24
54E0607	week 6
54E0609	week 12
5500971	week 9
5501025	week 12 and month 3 in study 189B
57B0232	week 6
64E0024	month 12 in study 189B
74E1031	week 9
76A0171	week 20
77E0181	week 9
78E0632	week 16 and month 3 in study 189B
7990307	week 24
7990310	week 6
79E0263	week 24
80E0200	12 and month 3 of study 189B
80E0268	week 6
80E0270	week 24
16G1021	week 24
42B0156	week 24 and month 1 of study 189B
54E0025	week 20
54E0223	week 9
5500972	week 6 and month 6 in study 189B
57B0229	week 6
57B1009	week 12
57B1010	week 6
71E0066	week 16
76A0174	week 12
79E0441	week 6
79E0442	week 12

5. In clinical trial 189 how long were patients followed after they completed 24 weeks of therapy?

6. In the experiment where the stability of MAC in drug containing isolator tubes was conducted please explain why 0.4 ug/ml azithromycin was evaluated. Higher concentrations of azithromycin – are obtained in cells than clarithromycin where 4.0 ug/ml was tested in this experiment.

7. There are two major concerns regarding the validation and standardization of the azithromycin susceptibility testing method and the potential establishment of azithromycin breakpoints. Issues that must be discussed are:

   a. What susceptibility testing methods are you proposing to validate and standardize? Please keep in mind that approximately 70% of the clinical laboratories in the U.S. [redacted] 30% of the laboratories use the agar dilution method. As such, the Division strongly recommends that azithromycin susceptibility testing be validated using these two methods.

b. To adequately characterize the cross resistance pattern between clarithromycin and azithromycin the susceptibility testing method for clarithromycin currently under evaluation should be used [redacted] to determine clarithromycin MIC values.

If you have any questions, please contact me at (301) 827-2387.

/S/

Diana Willard
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

HFD 590
WILLARD

Memorandum of a Teleconference

Meeting Date: April 14, 2000

Application: NDA 50-730/S-005 and S-006
Zithromax (arithromycin) Tablets, 600 mg

Sponsor: Pfizer Central Research

Subject: Microbiology Issues/Questions

Attendees:

Pfizer:

Michael Dunne, M.D.	GCTL, Clinical Research
Dearborn Edwards, M.D.	Clinical Research
Michael Zelasky	Biometrics Team Leader
James Retsema, Ph.D.	Discovery Microbiology
Christopher DuBord	Information Technology
Ronald I. Trust, Ph.D.	Regulatory Strategy and Registration

FDA:

Marc Cavaillé-Coll, M.D., Ph.D.	Team Leader/Medical Officer, HFD-590
Joyce Korvick, M.D., M.P.H.	Medical Officer, HFD-590
Linda Gosey	Microbiologist, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

Supplemental New Drug Applications submitted to NDA 50-730 on January 13, 2000 propose 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, an indication for the same dosage to be used in combination with other anti-mycobaterial agents to treat pulmonary MAC infections in non-HIV infected patients is proposed.

An April 6, 2000 facsimile transmission (FAX) from the Division outlined several microbiology questions/issues to be discussed during this teleconference.

An April 14, 2000 FAX from Pfizer responded to several items in the Division's April 6, 2000 FAX.

Teleconference Objectives

- To discuss questions/issues in the Division's April 6, 2000 FAX.
- To outline the basis of a future teleconference to discuss the efficacy data submitted with these supplements.

Discussion

Below are the questions from the Division's April 6, 2000 FAX (in bold) followed by the teleconference discussion:

1. **Were clarithromycin MICs determined on the MAC isolates obtained from clinical trials [redacted] What susceptibility testing method was used to determine these MIC values?**

   Clarithromycin MICs were not determined on the MAC isolates obtained from these clinical trials. Microbiology methods utilized for these trials are outlined in the microbiology section of the supplement on page 188, Appendix I.

2. **In clinical trial 189, was ethambutol susceptibility testing conducted against the MAC isolates?**

   No susceptibility testing for ethambutol was conducted against the MAC isolates. Pfizer stated that no validation breakpoints for ethambutol were available.

3. **In the data files, individual azithromycin and clarithromycin MICs were expressed (i.e., MIC 6.7 ug/ml, 9.4 ug/ml). How were these individual MICs converted into the MIC categories described in the various tables found in Volume 11, pages 9-16?**

   For the tables described in Volume 11, pages 9-16, relevant MICs were pooled into categories such as >4-8 and >8-16. The method employed is described in the microbiology section of the supplement on page 188, Appendix I.

4. **Please provide the MICs on the MAC isolates recovered at the following time points:**

Study 189 Patient #	Time point
31A0053	week 9
31A255	month 18 and 19 in study 189B
32A0015	week 6
42B006	week 9
42B0090	week 12
42B0175	week 20
42E120	week 9
54E0026	week 16
54E0079	week 12
54E0083	week 20
54E0228	week 24
54E0607	week 6
54E0609	week 12
5500971	week 9
5501025	week 12 and month 3 in study 189B
57B0232	week 6
64E0024	month 12 in study 189B
74E1031	week 9
76A0171	week 20
77E0181	week 9
78E0632	week 16 and month 3 in study 189B
7990307	week 24
7990310	week 6
79E0263	week 24
80E0200	12 and month 3 of study 189B
80E0268	week 6
80E0270	week 24
16G1021	week 24
42B0156	week 24 and month 1 of study 189B
54E0025	week 20
54E0223	week 9
5500972	week 6 and month 6 in study 189B
57B0229	week 6
57B1009	week 12
57B1010	week 6
71E0066	week 16
76A0174	week 12
79E0441	week 6
79E0442	week 12

Pfizer stated that the MIC values requested above will be submitted. Ms. Gosey requested that Pfizer provide a timeline for submission of these data.

Pfizer clarified that MICs for any patient classified as either a therapeutic failure or that had experienced a relapse were not determined.

It was noted that Patient 42B0061 was inadvertently listed as 42B006 in the April 6, 2000 FAX.

Ms. Gosey noted that no MICs were provided for Patient 7990307, even though this patient had positive cultures throughout the study. Pfizer stated that because this patient never relapsed, no MICs were determined. Data currently available for this patient are provided on page 11, in Appendix V, Table 17.2 in the microbiology section of the supplement.

5. **In clinical trial 189, how long were patients followed after they completed 24 weeks of therapy?**

Table 7.2 from Appendix III of the microbiology section of the January 13, 2000 submission, also provided in Pfizer's April 14, 2000 FAX to the Division, detailed averages for length of follow-up for the three treatment groups in clinical trial 189.

If a patient had a positive culture at the end of clinical trial 189, that patient was not eligible for enrollment in clinical trial 189b. There is no follow-up data beyond the 24 weeks for patients in clinical trial 189 that did not enroll in clinical trial 189b.

If possible, the Division would like MICs be provided for any patient that had a positive culture at any time in clinical trial 189b. In addition, if a SAS transport file containing these data is available, the location of these data in the SAS file should be clarified.

6. **In the experiment where the stability of MAC in drug containing isolator tubes was conducted, please explain why 0.4 ug/ml azithromycin was evaluated. Higher concentrations of azithromycin are obtained in cells than clarithromycin where 4.0 ug/ml was tested in this experiment.**

In this experiment, 0.4 ug/ml is the expected peak concentration of azithromycin in plasma.

7. **There are two major concerns regarding the validation and standardization of the azithromycin susceptibility testing method and the potential establishment of azithromycin breakpoints. Issues that must be discussed are:**

a. **What susceptibility testing methods are you proposing to validate and standardize? Please keep in mind that approximately 70% of the clinical laboratories in the U.S. [redacted] 30% of the laboratories use the agar dilution method. As such, the Division strongly recommends that azithromycin susceptibility testing be validated using these two methods.**

As this supplement proposes to add a treatment indication to the label, breakpoints will need to be established using a validated testing method. This information will be included in the microbiology section of the label. Stating that it is a simpler protocol to carry out, Pfizer indicated their preference for [redacted] method.

Ms. Gosey stated that although it is Pfizer's decision, whatever method is chosen should be user friendly to the clinical laboratories that conduct the tests in the United States. She emphasized that susceptibility methods must first be validated prior to establishing breakpoints. The Division indicated that the establishment of breakpoints can be on-going after an action is taken on these supplements. Ms. Gosey stated that the breakpoints chosen by the FDA may be different from those chosen by NCCLS.

b. **To adequately characterize the cross-resistance pattern between clarithromycin and azithromycin, the susceptibility testing method for clarithromycin currently under evaluation should be used [redacted] to determine clarithromycin MIC values.**

Further discussion between the Division and Pfizer regarding this issue is needed and will occur at a later date.

Efficacy Analysis

Dr. Korvick stated that a preliminary review of the efficacy data raised questions regarding whether the primary endpoint, sterility of MAC from the blood, had been met. Study 189 failed to demonstrate that a regimen of azithromycin 600 mg plus ethambutol is equivalent to the comparator regimen of clarithromycin plus ethambutol. As a result, in order to argue that the azithromycin 600 mg regimen is effective, it would need to be demonstrated that the regimen of azithromycin 600 mg plus ethambutol can be expected to perform significantly better than ethambutol given alone.

It was agreed that a teleconference would be scheduled to discuss this issue.

Summary

The questions/issues from the Division's April 6, 2000 FAX were discussed. It was agreed that further discussion between the Division and Pfizer would occur regarding establishment of breakpoints.

A teleconference will be scheduled to discuss interpretation of the efficacy data submitted in support of these supplements.

Minutes Preparer: /S/
Diana Willard

Concurrence, Meeting Chair: /S/ 5/9/00
Marc Cavaillé-Coll, M.D., Ph.D.

HFD-590
D. Willard

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: May 10, 2000

TO: Dr. Trust

ADDRESS: Pfizer Central Research
Eastern Point Road
Groton, CT 06340

TELEPHONE: 860-441-6991

FAX: 860-441-0870

FROM: Diana Willard

APPLICATION: NDA 50-730

SUBJECT: Comments for May 19, 2000 teleconference

Please refer to your NDA 50-730 for Zithromax. We provide the following comments in preparation for our May 19, 2000 teleconference:

Study 189 has failed to demonstrate that a regimen of azithromycin 600 mg plus ethambutol is equivalent to the comparator regimen of clarithromycin plus ethambutol. As a result, in order to argue that the azithromycin 600 mg regimen is effective, one would need to be able to show that the regimen of azithromycin 600 mg plus ethambutol can be expected to perform significantly better than ethambutol given alone. Do you have any evidence that would support this conjecture?

Please be aware that we do not consider it appropriate to compare the azithromycin 600 mg plus ethambutol arm to the azithromycin 250 mg plus ethambutol arm that was dropped from the study during the interim analysis.

If you have any questions, please contact me at (301) 827-2387.

Diana Willard
Regulatory Health Project Manager
Division of Special Pathogen and
Immunologic Drug Products

HFD-590/D Willi

Memorandum of a Teleconference

Meeting Date: May 19, 2000

Application: NDA 50-730/S-005 and S-006
Zithromax (arithromycin) Tablets, 600 mg

Sponsor: Pfizer Central Research

Subject: Review Issues

Attendees:

Pfizer:

Michael Dunne, M.D.	GCTL, Clinical Development
Dearborn Edwards, M.D.	Clinical Development
Michael Zelasky	Biometrics Team Leader
Rebrecca Benner, Ph.D.	Biometrician
Douglas Simmons	Biometrician
James Retsema, Ph.D.	Discovery Microbiology
Ronald I. Trust, Ph.D.	Regulatory Affairs

FDA:

Marc Cavaillé-Coll, M.D., Ph.D.	Team Leader/Medical Officer, HFD-590
Joyce Korvick, M.D., M.P.H.	Medical Officer, HFD-590
Karen Higgins, Sc.D	Acting Team Leader/Mathematical Statistician, HFD-725
Michael Elashoff, Ph.D.	Biostatistician, HFD-725
Linda Gosey	Microbiologist, HFD-590
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacologist and Biopharmaceutist, HFD-880
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

Supplemental New Drug Application (sNDA) 005, submitted to NDA 50-730 on January 13, 2000, proposes 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, an indication for the same dosage to be used in

combination with other anti-mycobaterial agents to treat pulmonary MAC infections in non-HIV infected patients is proposed in sNDA 006, also submitted January 13, 2000.

A May 10, 2000 facsimile transmission (FAX) from the Division contained comments from Dr. Silliman, statistical reviewer for these supplements, to be discussed during this teleconference.

A May 18, 2000 FAX from Pfizer (Attachment 1) contained previously submitted information that Pfizer believed would be pertinent to the discussion.

Teleconference Objectives

- To discuss questions/issues outlined in the May 10, 2000 FAX.
- To discuss review issues associated with the efficacy data submitted with these supplements.

Discussion

Statistical Issues

Dr. Korvick began by stating that the May 10, 2000 FAX contained comments pertaining to Dr. Silliman's statistical review of the pivotal study. The clinical and microbiology reviews of these supplements are on-going.

The Division stated that although azithromycin does not demonstrate equivalence to the active control in Study 189 for the primary analysis, this does not necessarily mean that these supplements can not be approved. The burden for Pfizer is to provide a written argument using either historical data or a comparison between azithromycin and placebo demonstrating that azithromycin is more efficacious than placebo.

Dr. Elashoff pointed out that the protocol was very specific about planned analyses to conserve type I error (alpha). Given this, it is difficult to place much weight on the unplanned comparison between the two dose groups.

Pfizer stated that the only way to do a comparison between the 600 mg/day and 250 mg/day azithromycin arms would be to conduct an ad hoc analysis and adjust the alpha accordingly. Dr. Elashoff stated that once a study is completed, a completely new analysis plan is not of great value in terms of making regulatory decisions.

Pfizer stated that multiple analyses were conducted demonstrating that the 250 mg/day azithromycin arm is not as efficacious as the 600 mg/day azithromycin arm. The fact that these analyses all point in the same direction may be of supportive value. Dr. Korvick stated that while it is difficult to interpret these data from a statistical point of view, from

a clinical perspective it may be possible to use these data for hypothesis generating purposes.

The data submitted in these supplements defines confidence bounds wider than the pre-specified limits. Noting that the burden of proof is on azithromycin to demonstrate equivalence to clarithromycin, Dr. Elashoff stated that either Pfizer did not enroll enough patients to achieve sufficient power to demonstrate equivalence or azithromycin is indeed inferior to clarithromycin. Pfizer stated that in order to have sufficient power to meet the pre-specified boundary the full cohort of patients was needed, i.e., 75 patients per arm. A number of patients either died or dropped out for other adverse events, making it difficult to attain a sufficient number of evaluable patients. With the number of patients actually enrolled, there was approximately 60% power to demonstrate equivalence between azithromycin and clarithromycin. The pre-specified primary test may now be suspect for reasons unforseen when the study was started.

Death Rates

Pfizer noted that the analysis submitted with the supplements showing the number of deaths at the end of the study is different from the analysis containing deaths on page 2 of the May 10, 2000 FAX (page 54 from Study Report 066-189/189B). Pfizer clarified that the page 54 analysis provides week 24 sterilization rates from the intent-to-treat analysis using alternative endpoint definitions.

Missing Data

Pfizer stated that one of the questions raised as the protocol was being written was how to present missing data. For example, if a patient died before week 24, should that patient be classified as a failure or carried forward for inclusion in the final analysis. The other option for this patient would be to "carry backward" his/her data. In the original pre-specified analysis plan, the methods employed for missing data were outlined.
Dr. Elashoff stated that Pfizer's approach to handling missing data in Study 189 appears reasonable. Various ways of viewing the data were presented and all the analyses lean in the same direction.

Azithromycin plus Ethambutol versus Azithromycin Alone

Pfizer noted that the Division's May 10, 2000 FAX suggested submitting data demonstrating that 600 mg/day azithromycin plus ethambutol is more effective than ethambutol alone. Published articles detailing results of studies using azithromycin plus ethambutol versus azithromycin alone could potentially support an argument for approval of these supplements.

Division Recommendations

Dr. Korvick recommended that Pfizer submit a convincing argument regarding the risk/benefit ratio of the proposed azithromycin treatment needs to be clearly delineated. This argument should include data demonstrating that the proposed treatment is better

than placebo or detail how the proposed azithromycin treatment is similar to the approved clarithromycin treatment.

The Division emphasized that if Pfizer chooses to submit historical data as part of an argument for approval, the comparability of patients enrolled in Study 189 to the historical population(s) chosen need to be addressed. In addition, any differences in endpoints and definitions need to be addressed to ensure that the comparisons are justified.

Published literature of azithromycin plus ethambutol versus azithromycin alone studies could also be submitted.

Colony Forming Units

Dr. Korvick noted that with the low number of colony forming units (CFUs) in this study, it may not be possible to demonstrate a log change before and after treatment for some patients. Pfizer should submit a written statement regarding how to address such low numbers of CFUs.

Mortality Rates

Pfizer noted that there was no difference in mortality rates between arms in Study 189. Dr. Korvick stated that as she has not reviewed that aspect of the data, this issue could be a topic for later discussion.

NCCLS Methodologies

Pfizer stated that proposed NCCLS methodologies establishing breakpoints for MAC are available. Ms. Gosey requested that a copy of the NCCLS proposed methodologies be submitted along with Pfizer's proposal.

Summary

The Division stated that although azithromycin does not demonstrate equivalence to the active control in Study 189 for the primary analysis, this does not necessarily mean that these supplements can not be approved. The burden for Pfizer is to provide a written argument using either historical data or a comparison between azithromycin and placebo demonstrating that azithromycin is more efficacious than placebo. Other supporting documents, such as published literature of azithromycin plus ethambutol versus azithromycin alone studies could also be submitted.

NDA 50-730/S-005 and S-006
May 19, 2000

Minutes Preparer:
/S/
Diana Willard

Concurrence, Meeting Chair:
/S/ 6/6/00
Marc Cavaillé-Coll, M.D., Ph.D.