CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-784

Administrative Documents

Item 16

DEBARMENT CERTIFICATION
[FD&C Act 306(k)(1)]

ZITHROMAX® Film-Coated Tablets 500 mg (NDA-50-784)
ZITHROMAX® for Oral Suspension (NDA-50-710) Community Acquired Pneumonia

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ronald J Tenant — June 15, 2001

Signature of Company Representative — Date

No exclusivity determination is applicable, as per "Guidance for Industry and Reviewers, Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act, section II 3. b.

FDA Links Searches Check Lists Tracking Link Calendars Reports Help

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

NDA Number:	050784	**Trade Name:**	ZITHROMAX (AZITHROMYCIN) 500MG TABLET
Supplement Number:	000	**Generic Name:**	AZITHROMYCIN
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
Original NDA Action Date:	7/27/01		

Indication # 1 Acute bacterial exacerbatio of chronic bronchitis

Comments (if any): acute bacterial exacerbation of chronic bronchitis is not a pediatric disease.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	17 years	Waived	

This page was last edited on 5/16/02

/S/ /S/

Signature Date

Team Leader Memorandum
NDA 50-784

From: John Alexander, M. D., M. P. H.
Medical Team Leader
Division of Anti-Infective Drug Products (DAIDP)

Applicant: Pfizer, Inc.
Product Name: Zithromax® Tri-Pak™
Active Ingredient: Azithromycin
Formulation: 500-mg Tablets

Submission Date: July 27, 2001
Memorandum Date: May 23, 2002

Zithromax (azithromycin) is an azalide antibiotic currently marketed in the United States. Zithromax is approved for treatment of acute bacterial exacerbation of chronic obstructive pulmonary disease (AECB) due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. It has a variety of other indications in adults, including community-acquired pneumonia, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections. The formulation used in adults is a 250-mg tablet. The dose regimen for these infections is: 500 mg (2 tablets) in a single dose on day 1, followed by 250 mg (1 tablet) on days 2 through 5. This 5-day dose regimen is marketed in a blister package known as the Z-Pak.

NDA 50-784 is an application for a new formulation of azithromycin, a 500-mg tablet. This new formulation is given in a 3-day dose regimen, 500 mg (1 tablet) daily for 3 days. Both the 3-day and 5-day regimens of azithromycin provide the same total dose of 1500 mg. Charles Bonapace, Ph. D., provides a thorough discussion of the results of pharmacokinetics (PK) studies in his Biopharmaceutics review. The PK data are somewhat limited, because of limited sampling times and the long half-life of azithromycin. However, based on the modeled PK results, the AUC_{0-120} results were similar for the two dose regimens. Therefore, similar PK profiles and the clinical data for the 5-day regimen provide some supportive evidence for approval of the 3-day regimen.

The NDA for Zithromax® Tri-Pak™ indication AECB,

Study A0661013 was the pivotal trial for the AECB indication. This was a double blind, double-dummy, randomized, multi-center, international trial comparing the 3-day regimen of azithromycin with clarithromycin 500 mg twice daily for 10 days. The primary endpoint for this trial was clinical outcome at the follow-up visit (days 21-24). There were several challenges in the review of this study. The efficacy data from 3 investigators were excluded because of concerns about data integrity. The Division of Scientific Investigations was involved in the review of these and other study sites. Discrepancies in the clinical outcomes for a random sample of patients led the medical reviewer to individually review all case report forms. In the end, the clinical outcomes, as judged by the medical reviewer, were remarkably similar to the applicant's results. In the MITT population of 304 patients, the medical reviewer reported clinical cure rates of 125/147 (85%) in the azithromycin group and 129/157 (82%) in the clarithromycin group. The 95% confidence interval for the difference in cure rates between treatment arms was (-6%, 12%). The clinical outcomes at follow-up for patients with a baseline pathogen are shown in the table below.

Baseline Pathogen	**Azithromycin**	**Clarithromycin**
S. pneumoniae	29/32 (91%)	21/27 (78%)
H. influenzae	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

The results of this trial demonstrate equivalence between the 3-day regimen of azithromycin and the approved clarithromycin regimen. Although not powered to demonstrate equivalence in subjects with a baseline pathogen, the pathogen specific cure rates are roughly comparable between treatment arms. There are sufficient numbers of these three pathogens to allow the same indication for the 5-day and 3-day regimens of azithromycin.

The safety of the 3-day regimen was evaluated in 2547 azithromycin-treated patients and 2466 comparator patients in phase 2-4 trial of this formulation. Overall, the safety profile for the 3-day regimen appeared similar to those labeled adverse events for the 5-day regimen of azithromycin. Treatment-related adverse events occurring in more than 1% of azithromycin-treated patients were diarrhea (3.5%), nausea (2.9%), and abdominal pain (2.0%). The rates of these events (3.2%, 2.5%, and 1.7%, respectively) in the comparator group were comparable. Less common treatment-related adverse events were similar to those already listed in the package insert for the 5-day regimen. Rates of discontinuations due to adverse events were comparable in the azithromycin and comparator patients. Discontinuations due to treatment-related adverse events were reported in 0.4% of the azithromycin group and 1.4% of comparator patients. Laboratory studies were performed in a smaller subset of patients. Laboratory studies were performed in 1140 azithromycin-treated patients and 963 comparator patients. Again, the laboratory adverse events noted in the trial were similar to those in the package insert for

the 5-day regimen. The medical officer reviewed all serious adverse events and deaths in her review. None of the deaths were considered related to study drug treatment.

The risk benefit analysis supports approval of NDA 50-784. The 3-day regimen of azithromycin is being approved for the treatment of acute exacerbation of chronic obstructive pulmonary disease. Information for the 500-mg tablets was added to the existing package insert for the 250-mg tablets and pediatric oral suspensions. In the negotiations of the package insert, the CLINICAL PHARMACOLOGY section of the label was updated, based on the information provided in labeling supplements for the 250-mg tablet (NDA 50-711/S-009) and pediatric oral suspensions (NDA 50-710/S-011). The applicant was asked to modify the CLINICAL PHARMACOLOGY information in the package insert for other formulation of Zithromax (NDA's 50-670, 50-693, and 50-733) using the label for this NDA as a template.

Another unique aspect of this application was the effort required for review of the carton and container labeling for this product. This product will be distributed in a blister package that has ample room for text. The final text for the blister packages and container were reviewed by the chemistry and medical reviewers, in consultation with representatives of the Division of Drug Marketing, Advertising, and Communications. DDMAC assisted the Division in assuring that information on the blister package for this product was presented in a fair and balanced manner. The applicant was asked to use the blister package for this NDA as a template for modifications to the Z-Pak carton and container labeling.

Finally, the Division of Anti-Infective Drug Products (DAIDP) and the Office of Drug Safety (ODS) reviewed the proposed trade name. DAIDP has chosen to accept the name, Zithromax® Tri-Pak™. Originally, the applicant proposed [redacted] as the name for this product. There were concerns on the part of DAIDP and the Division of Medication Errors and Technical Support (DMETS) in ODS. Specifically, it was considered inappropriate to include the [redacted] as part of the name. There was the potential for multiple Z-Paks to be dispensed in error. The Division was concerned that the similarity to Z-Pak would lead to prescriptions of the [redacted] be given in place of the Z-Pak for indications other than AECB. In addition, there did not appear to be the need for a blister package, when it was simple enough for a pharmacist to dispense three 500-mg tablets of azithromycin with instruction to take one tablet once a day. The Division conveyed these concerns to the sponsor.

The applicant proposed the name Tri-Pak to address the concerns raised by DMETS and DAIDP. DMETS made recommendations for modifications to the packaging and increase prominence of the Zithromax® name. The applicant made the requested changes to the carton and container labels, and agreed to use Zithromax® Tri-Pak™ as the product name in advertising. The applicant was also asked to promote use of the full name in prescribing the new product. In accepting this name, DAIDP recognizes the efforts of the applicant to address the Agency's concerns. The applicant appears willing to make good faith efforts to promote use of the full name to decrease medication errors.

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/s/

John Alexander
5/24/02 03:11:29 PM
MEDICAL OFFICER
Team Leader Memorandum for Approval of Zithromax Tri-Pak

Janice Soreth
5/24/02 03:14:36 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: May 24, 2002

APPLICATION NUMBER: NDA 50-784
Zithromax TRI-PAK (azithromycin), 500 mg Tablets

BETWEEN:

Name: Ronald I Trust
Phone: 860-732-6991
Representing: Pfizer Inc.

AND

Name: Judit Milstein, Regulatory Project Manager
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Shelf life for the product

During a telephone call on May 23, 2002, the sponsor was informed that a shelf life of 3 years is granted for this product.
Ron Trust concurred with the Agency's decision.

/S/

Judit Milstein
Regulatory Project Manager

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/s/

Judit Milstein
5/24/02 11:18:33 AM
CSO

Frances LeSane
5/24/02 01:43:38 PM
CSO

David Katague
5/24/02 01:50:19 PM
CHEMIST

TELECONFERENCE MINUTES

Meeting Date: November 12, 1997
Time: 9:00 AM
Location: Conference Room S-314
Application: IND [redacted] /IND- [redacted]
Drug: Zithromax
Sponsor: Pfizer
Type of Meeting: Guidance
Meeting Chairs: Dr. Mercedes Albuerne
Meeting Recorder: Mr. Jose R. Cintron, R.Ph., M.A.

FDA DAIDP Attendees:
Dr. Gary Chikami, Division Director
Dr. Mercedes Albuerne, Clinical Team Leader
Dr. Gino Girardi, Medical Officer
Dr. Frank Pelsor, Team Leader Biopharm Reviewer
Dr. He Sun, Biopharm Reviewer
Mr. Jose Cintron, Project Manager

Pfizer's Attendees:
Dr. Fred Duncanson, Clinical
Dr. Michael Dunne, Clinical
Dr. George Foulds, Biopharm
Dr. Dial Hewlett, Clinical
Dr. Ann Kolokathis, Medical
Ms. Malvina Laudicina, Regulatory Affairs
Mr. Robert Clark, Regulatory Affairs

Pfizer submitted a proposal for Division to consider the use of pharmacokinetic data in support of a reduction in duration of therapy from 5 to 3 days. The total, cumulative dose of Zithromax (azithromycin) would be the same for the three day regimen (1.5 grams orally) as is currently approved for the 5 day regimen. A patient would receive 500mg once/day for three days rather than 500mg on day 1, followed by 250mg on days 2-5.

- The current indications for which short-course Zithromax would be indicated are AECB, [redacted]

- Pfizer wishes to use PK/PD data to support changing the dosage and administration section of the labeling from the current: 500mg orally the first day, 250 mg orally days 2-5 to: 500mg orally for three days. Hence, the total dose remains the same, the duration is shortened.

- Dr. Girardi stated that in the current version of our "Guidance to Industry" document, it is stated that "Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens or dosage forms as long as blood levels and exposure are not very different. In cases where the pharmacokinetics of a new regimen is very similar to the previously approved one, no further clinical trial support may be needed. In this situation, PK data is used to bridge the results of the new dose, regimen or dosage form to the efficacy trial results."

- Dr. Girardi suggested that they also do clinical studies, preferably comparing themselves to themselves (3 vs. 5 days). A single study for each indication might be acceptable.

- Tolerability was also raised as a concern pointing to the need to do clinical trials. When Zithromax is dosed as a 2-gram single-dose therapy for gonorrhea, about 33% of patients experience nausea/vomiting. Safety data would be important to gather in relation to a higher C-max seen with the three-day regimen.

- The three-day regimen is approved in Europe. Any clinical study done for licensing a short-course therapy should be done in North America, especially for safety reporting. Adverse event reporting is generally lower in Europe.

Minutes Preparer: Jose R. Cintron, R.Ph., and M.A.
Senior Regulatory Management Officer

cc:
IND [redacted]
HFD-520/Div. Files
HFD-520/Div.Dir/GChikami
HFD-520/Medical Officer/GGirardi
HFD-880TL Biopharm/FPelsor
HFD-880/Biopharm/HSun
HFD-520/ Project Manager/JCintron

Drafted by: jrc/December 17, 1997
Initialed by: JRC
Final:
File name: C:\\data\wordfiels\minutes\AziTEL12Nov1997.doc

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/s/

Jose Cintron
7/6/01 10:13:32 AM
CSO

Meeting Minutes November 12, 1997

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 22, 1998

Time: 11:00 AM-12:30 PM (industry)

Location: CORP S-300

Application: IND — /IND —

Drug: Zithromax (azithromycin)

Type of Meeting: Guidance

Meeting Chair: Dr. Gary Chikami, Director

FDA Attendees, Titles, and Office/Division:
HFD-520/Medical Team Leader/MAlbuerne
HFD-520/Medical Officer/NMoledina
HFD-520/Medical Officer/ADavidson
HFD-520/Microbiology/ Team Leader/ASheldon
HFD-725/Biostatistics Team Leader/DLin
HFD-880/ Team Leader Biopharmaceutics/FPelsor
HFD-880/ Biopharmaceutics Reviewer/HSun
HFD-880/ Biopharmaceutics Reviewer/KUhl
HFD-520/ Project Manager/JCintron

Pfizer Attendees and titles:
Jose Barruecos, Ph.D./Clinician
Robert Clark/ Regulatory Affairs
Frederick Duncanson, M.D./Clinician
Mike Dunne, M.D./Clinician
Malvina Laudicina/Regulatory Affairs
Jial Hewlett/Clinician
Helen Bhattacharyza/Statistician

Background:
Pfizer submitted a proposal to the Division to consider the use of pharmacokinetic data in support of a reduction in duration of therapy from 5 days to 3 days. The total, cumulative dose of azithromycin would be the same for the three-day regimen (1.5 grams orally) as is currently approved for the 5-day regimen. A patient would receive 500 mg once/day for 3 days rather than 500 mg on day 1, followed by 250 mg on days 2-5. The current indications for which short-course Zithromax would be indicated are AECB

The proposal submitted is based on the unique pharmacokinetics and pharmacodynamics of Zithromax. The safety and efficacy of the three-day regimen is supported by a safety database of 29 U.S.-sponsored international safety studies and 11 U.S.-sponsored international efficacy studies conducted according to GCP. The 3-day dosing regimens were studied in populations and diseases comparable to the U.S. population and utilizing outcome assessments comparable to those recommended in FDA's Guidance documents.

Meeting Objectives: To obtain agreement from the FDA to support the inclusion of an alternative 3-day regimen [redacted]

Discussion Points:

Pfizer would like know if this proposal is adequate to prepare a supplemental New Drug Application to support approval for the three-day dosing [redacted]

Pfizer proposed the following issues for discussion:

- azithromycin (Zithromax) 500 mg/day over 3 days as an alternative regimen for the treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (Adult),
- [redacted]
- [redacted]

Decisions (agreements) reached:

- Dr. Dunne (Pfizer) gave a brief presentation of the proposal for the package insert for Zithromax to add 3-day dosing regimen [redacted] acute exacerbation of chronic obstructive pulmonary disease (Adult), [redacted] He indicated that the data come from international studies, especially European studies where the 3-day regimen is already approved.
- Dr. Chikami (FDA) commented that the proposal presented at the meeting seemed fairly reasonable. [redacted]

Dr. Chikami explained to the sponsor that if efficacy is shown — then AECB indication could be granted to.

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- Dr. Albuerne (FDA) indicated to the sponsor that the data should be analyzed by gender, age, and race. Under the new FDAMA rules, failing to submit these information could result in a "refuse to file" the application.

BIOPHARMACEUTIC'S COMMENTS:

- Dr. Sun indicated that to claim the 3-day and 5-day dosage regimens are equivalent in terms of 10-day treatment exposure, the sponsor uses: (1) the role of PMNs in carrying the drug to the site of infection (their assumption is that when given higher dose, PMNs uptake more drug, so the total amount carried to the site of infection is similar); and (2) tissue levels, not plasma levels, is the measure of total drug exposure. Clinical pharmacology questions in this regard are:

    - ♦ To calculate PMN/plasma concentration ratios at various plasma concentrations based on the pharmacokinetic data available (perhaps from study 066-087)

    - ♦ To provide any experimental or theoretical data to demonstrate that the total tissue (e.g. skin, lung, MEF) concentrations (or exposures) are similar for the 3-day and 5-day regimen

- The C_{max} is higher with the 3-day regimen (0.35 ug/ml) than with the 5-day regimen (0.1-0.15 ug/mL). The half-life of the drug is longer than the dose interval (68 hours vs. 24 hours) and drug accumulation in the body is expected. Therefore, it is important to know what the C_{max} and AUC will be if the half-life of azithromycin is increased in patients who have reduced renal, hepatic, and/or bile clearance.

    - ♦ Any observational data or simulation data available to compare azithromycin plasma concentration-time profile in patients who have decreased CL when given the 3-day or 5-day dose regimen should be provided.

- In William A. Craig's paper (which is the most favorite supporting paper the sponsor is using), it is concluded that AUC/MIC is a good pharmacodynamic parameter that predicts clinical efficacy for azithromycin because of extended post antibiotic effect (PAE).

    - Is PAE concentration, incubation/contact time, or AUC/dose dependent (in vitro and/or in vivo animal models) for these bacteria that are responsible for the labeled indication?

BIOSTATISTICIAN'S COMMENTS:

- Dr. Lin (FDA) asked for clarification for the test of cure date for the clinical response rate, .

    - The sponsor indicated that the detailed information will be included in the future NDA submission.

- In the future NDA submission, the reasons why patients droped out of the study should be provided.

    - The sponsor indicated that the detailed information will be included in the future NDA submission.

MEDICAL OFFICER'S COMMENTS:

- Pfizer was reminded of the Phase 4 commitment to evaluate the potential of Zithromax to cause ocular phospholipidosis. Specifically, this study should be performed on patients who are treated at a dose of 12 mg/kg/day for 5 days. The sponsor indicated that the detailed information will be submitted in December 1998.

- A detailed report for each of the studies, including a list of the pathogens, should be submitted to the application .

Unresolved issues or issues requiring further discussion:
Actions Items: None

Minutes Prepared by: Jose R. Cintron, R.Ph., M.A.

Chair Concurrence: Gary Chikami, M.D.

Attachments/Handouts: Attendance sheet, Pfizer's overhead presentation

cc:
IND [redacted]

Concurrence Only:

HFD-520/Div. Files
HFD-520/Medical Officer/NMoledina
HFD-520/Medical Officer/ADavidson
HFD-520/Microorganism Team Leader/ASheldon
HFD-520/ Project Manager/JCintron
HFD-520/AEvans
HFD-725/Biostatistics Team Leader/DLin
HFD-880/ Team Leader Biopharmaceutics/FPelsor
HFD-880/ Biopharmaceutics Reviewer/HSun
HFD-880/ Biopharmaceutics Reviewer/KUhl
HFD-520/CPMS/JBona
HFD-520/TLMO/MAlbuerne

Drafted by: jrc/September, 25, 1998
Initialed by: jrc
final:

MEETING MINUTES

/s/

Jose Cintron
10/19/1998 09:10:57 AM

James Bona
10/19/1998 09:58:37 AM

He Sun
12/14/00 12:35:12 PM
PHARMACOLOGIST
Just got DFS reconnected upon returning. To sign off.

Frank Pelsor
12/15/00 08:08:54 AM
BIOPHARMACEUTICS

Mercedes Albuerne
12/26/00 03:53:38 PM
MEDICAL OFFICER

Nasim Moledina
1/2/01 07:49:31 AM
MEDICAL OFFICER

Daphne Lin
1/11/01 11:22:24 AM
BIOMETRICS

Gary Chikami
2/20/01 04:24:43 PM
MEDICAL OFFICER

Jose Cintron
3/2/01 07:48:13 AM
CSO

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 12, 2000

Time: 3:00 PM – 4:30 PM (industry)

Location: CORP S-300

Application: IND [redacted] /IND [redacted]

Drug: Zithromax (azithromycin)

Type of Meeting: End of Phase 2 Meeting

Meeting Chair: Dr. Gary Chikami, Director

FDA's Attendees, Titles, and Office/Division:
HFD-520/Medical Team Leader/MAlbuerne
HFD-520/Medical Officer/NMoledina
HFD-520/Microbiology/HSilver
HFD-725/Biostatistics Team Leader/DLin
HFD-830/Chemistry/JTimper
HFD-880/ Team Leader Biopharmaceutics/FPelsor
HFD-344/DSI/MThomas
HFD-520/ Project Manager/JCintron

Pfizer's Attendees and titles:
Frederick Duncanson, M.D./Clinician
Mike Dunne, M.D./Clinician
Ron Trust/Regulatory Affairs
Victor Clavelli/ Regulatory Affairs
Helen Bhattacharyza/Statistician

Background:

During a May 13,1999 meeting with the Division of Anti-Infective Drug Products, Pfizer presented an overview of Phase 4 international studies conducted between 1988 and 1998, and recently filed and approved French studies that could be used in support of the addition of new dosing regimens for the treatment of the indications sought. The sponsor had revised the design for the Division of Anti-Infectives Drug Products to review their submission and to give comments together on whether the application was fileable. Comments were provided to the sponsor at that time and Pfizer re-evaluated their development strategy.

Discussion and Recommendations:

- Dr. Dunne presented the restructured development program for the ZITHROMAX AD Program to the Division. The primary emphasis was on the proposed submission of new clinical studies to support the accelerated dosing (AD) claims. The Division Reviewers accepted the designs of the new protocols and the plan for shifting many of the international legacy studies to a non-supportive status, thereby contributing to the analysis for safety data only.

- Pfizer presented the details of how the submissions would be structured, including the positioning of the legacy studies. Many of these had been the subjects of a previous proposal to support the claims. Pfizer's revised strategy has placed many of these studies in a down-graded status for the purpose of safety reporting, whereas those studies judged to be supportive for the claimed indications were retained in the pivotal/supportive areas of the application. Therefore, some of the studies whose data may have been difficult to authenticate at the study sites would no longer be subject to DSI review.

- Dr. Chikami asked how many subjects would be described in the pivotal study section. Dr. Dunne indicated that approximately 300-500 subjects per indication would be provided, with several thousand subjects being described for safety. Pfizer will provide the actual breakdown by indication.

-

- The following claim structure was presented to and agreed to by the Division:

Adult Indications

Acute Bacterial Exacerbation of Chronic Obstructive Lung Disease

- The Division staff repeated a request made on previous occasions regarding a side-by-side comparison of 3-day and 5-day safety data.

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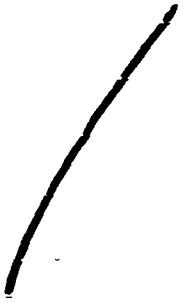
- Dr. Lin commented that one of the protocols (AZM-F-96-001) contained statistical analysis plans that utilized a 90% confidence interval (CI) methodology for determination of equivalence. Most of the protocols utilized a 95% confidence interval analysis. Dr. Bhattacharyya responded that Study 96-001 was originally analyzed by the methods defined by Pfizer's French affiliate office, based on the protocol-defined methodology using the 90% CI. However, for this application, the study would be reanalyzed using 95% CI. Dr. Lin also questioned the use of logistic regression for identifying baseline variables, which may influence outcome, as described in Protocol R-0581. Dr. Bhattacharyya responded that a revised statistical analysis plan would be provided. Pfizer will provide copies of the current statistical analysis plans for the pivotal studies. Dr. Lin mentioned later that the Division would like the opportunity to comment on the statistical plans in advance of the NDA submissions. Protocol R-0581, indicated that "multivariate statistical procedures (e.g.; logistical regression) will be used to identify baseline variables (prognostic factors) that may have some influence on the primary efficacy variable". If there is any intention to use any covariance-adjusted approach; the covariate should be specified in advance. Pfizer commented that they would identify them and include the details in the statistical analysis plan.

- 

- Mr. Silver requested confirmation of the zone diameter designated as sensitive for penicillin V (28 mm), the comparator used in clinical protocol AZM-F-96-001. Mr. Silver also recommended that any description of diagnostic tests (diagnostic Kits) for microorganism identification (such as serologic determinations) should be described in detail in the study reports for diagnostics kits, this

includes a description of the test, the manufacturer, and whether the assay kit is FDA-approved.
Clinical Protocol A066-1013 (Serology): Need the following information on the Serology Testing and the Urinary Antigen Testing for the atypical microorganisms and *Streptococcus pneumoniae*:

1. Provide a full description of the aforementioned testing methodologies;
2. Provide the Package Insert for the Diagnostic Kits used;
3. State if the Diagnostic Kits are FDA approved;
4. Provide the criteria for Positive Diagnosis; and
5. Describe the test result(s) and your conclusions.

- Mr. Silver provided an advanced draft of a Guidance Document for industry for the Development, Analysis and Presentation of Microbiological Data for Anti-infective Drug Products. Sponsors are encouraged to follow the Guidance in preparation of the Microbiology section of the NDA. [A copy of this Guidance is attached.]

- Pfizer informed the Division that azithromycin was recently approved in Japan. Pfizer's proposal is to provide only the Japanese labels, rather than the details of the local studies. The Division accepted the proposal.

- Pfizer proposed to provide information regarding source data to DSI which was acceptable to Dr. Thomas, of DSI. Pfizer committed to providing most of the remaining requested action items in the submission. An exception was the request to provide reasons why subjects in Study 93-007, who were seen at End-of-Therapy, may not have been seen at later time points. This was primarily a protocol issue, as subjects classified as cured at EOT did not have to return for the EOS visit. A diligent effort had been made to obtain this information, but without complete success. Dr. Lin stated that it would be helpful to have as much data as possible at the time of review, as she may consider performing a sensitivity analysis by imputing a response for the subjects who did not return for the follow-up visit. A line listing of the data available will be provided in the submission.

- Studies in which certain investigators may have questionable GCP compliance will have analyses run with and without their contributions to the data. Dr. Thomas said he was comfortable with this plan.

-

- In conclusion, the Division felt that the suitability of the package has been strengthened by the addition of new, robust, GCP-compliant studies.

Action Items from this Meeting:

1. Provide copies of statistical analysis plans for pivotal protocols.
2. Confirm the disk zone diameter designating sensitivity to penicillin V. [Note: subsequent review of the NCCLS methodology guidance confirms that as of the 1998 Guidance, the value of ≥28 mm was the correct disk diffusion susceptibility zone diameter for penicillin. The cutoff diameter for azithromycin is ≥ 18 mm.]

   Provide the following serology and other testing information in the new study protocols: describe in full the testing methodologies; submit the Package insert for the diagnostic Kit(s) used; state if the diagnostic kit(s) is FDA approved; describe the criteria for Positive Diagnosis; and describe the test results and your conclusion.

Issues Requiring Further Discussion: None

Action Items: None

/S/

Minutes Preparer: Jose R. Cintron, R.Ph., M.A.
Senior Regulatory Management Officer

/S/

Chair Concurrence: Gary Chikami, M.D.
Division Director

Attachments: None

cc:
IND
HFD-520/Div. Files
HFD-344/DSI/MThomas

Concurrence Only:
HFD-520/CPMS/FLeSane
HFD-520/TLMO/MAlbuerne

HFD-520/Div.Dir/GChikami
HFD-520/Medical Officer/NMoledina
HFD-520/ Microbiology Team Leader/ASheldon
HFD-520/Microbiology/HSilver
HFD-725/Biostatistics Team Leader/DLin
HFD-830/Chemistry/JTimper
HFD-880/ Team Leader Biopharmaceutics/FPelsor
HFD-520/ Project Manager/JCintron
HFD-520/AEvans

HFD-520/Medical Officer/NMoledina

Drafted by: jrc/April 30, 2000
Initialed by: JRC
Final:
File name: C:\\data\wordfiels\minutes\AziEP2April12, 2000.doc

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

/s/

Gary Chikami
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APPEARS THIS WAY
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MEMORANDUM OF MEETING MINUTES

Meeting Date: May 13, 1999

Time: 2:30 PM – 4:45 PM (industry)

Location: CORP S-300

Application: IND [redacted] IND [redacted]

Drug: Zithromax (azithromycin) [redacted]

Type of Meeting: Pre-NDA Meeting/Guidance

Meeting Chair: Dr. Gary Chikami, Director

FDA's Attendees, Titles, and Office/Division:
HFD-520/Medical Team Leader/MAlbuerne
HFD-520/Medical Officer/NMoledina
HFD-520/Microbiology/ Harold Silver
HFD-725/Biostatistics Team Leader/DLin
HFD-830/Chemistry/JTimper
HFD-880/ Team Leader Biopharmaceutics/FPelsor
HFD-344/DSI/MThomas
HFD-520/ Project Manager/JCintron

Pfizer's Attendees and Titles:
Robert Clark/ Regulatory Affairs
Frederick Duncanson, M.D./Clinician
Mike Dunne, M.D./Clinician
Malvina Laudicina/Regulatory Affairs
Helen Bhattacharyza/Statistician

Background:
Pfizer submitted a proposal to the Division to consider the use of pharmacokinetic data in support of a reduction in duration of therapy from 5 days to 3 days. The total cumulative dose of azithromycin would be the same for the three-day regimen (1.5 grams orally) as is currently approved for the 5-day regimen. A patient would receive 500-mg once/day for 3 days rather than 500 mg on day 1, followed by 250 mg on days 2-5. The current indications for which short-course Zithromax would be indicated are AECB, [redacted]

[redacted] The proposal submitted is based on the unique pharmacokinetics and pharmacodynamics of Zithromax. The safety and efficacy of the three-day regimen is supported by a safety database of 29 U.S.-sponsored international safety studies and 11 U.S.-sponsored international efficacy studies conducted according to GCP. The 3-day

dosing regimens were studied in populations and diseases comparable to the U.S. population and utilizing outcome assessments comparable to those recommended in FDA's Guidance documents.

Meeting Objectives:

1. To determine the acceptability of the proposed NDA development plan for azithromycin 3-day dosing regimen

2. To identify scientific and regulatory issues for and from the Food and Drug Administration's reviewing Division

3. To evaluate the applicant's plan relative to the Agency or Division issued Guidances.

4. To obtain an agreement from FDA on Pfizer's proposals.

Discussion Points:

- To clarify the filing package of Zithromax 3-day dosing to the Agency

- To obtain an agreement that the package is suitable for filing:

    a. Feedback requested on filing issues
    b. Feedback requested on approvability issues

- To update the Division on refinements from findings from study review pertinent to the Zithromax 3-day dosing:
    a. Findings from clinical studies
    b. Adding bronchitis studies
    c. Findings from site assessments

Decisions (agreements) reached:

- Dr. Dunne (Pfizer) presented Pfizer's proposal and issues that have been identified by Pfizer after the evaluation of the studies, sites, and investigators that were part of the proposal sent to the Division in September 1998, and will be part of the submission. During the discussion of these slides, a number of points were raised and discussed. A summary of those items is presented below.

-

- In the 91-020 study, Dr. Lin noted that there were fewer subjects at the end of therapy analysis compared to the follow-up analysis and a discussion ensued around the treatment of missing data. Pfizer will apply the proposed sensitivity analysis for handling missing data at EOT. A discussion of the methodology regarding missing subjects would also be included in the text of the reports.

- Dr. Thomas, the representative for the Division of Scientific Investigations (DSI), asked a number of questions and had some comments. Dr. Thomas stated that DSI's policy has been to recommend to the Reviewing Division not to accept data that could not be supported by source documentation. So if there were subjects for whom no source documentation was available, it may be necessary to run analyses by excluding these subjects. He offered to review the pivotal protocols and case report forms from studies to assess which source documents would be essential for each trial. Dr. Thomas indicated that in countries where oral consent was obtained, it would be helpful to FDA if the sponsor provided the local regulations regarding consent for human subjects in research as required by the Health Ministries in each country. It would also be useful to know what the local regulations were concerning study document retention. Dr. Thomas inquired if the sponsor could provide details of the circumstances that led the sponsor to believe that three investigators had lapses in GCPs. Pfizer replied that there would be a discussion of each circumstance in the text of the study reports. Pfizer conducted the PK studies in France, Germany, and two pediatric studies in the U.S. These studies have not been filed to the IND as of today. Dr. Thomas voiced his concern about the integrity of data that cannot be supported by adequate and accurate source documentation.

- Pfizer briefly discussed that the proposed to be marketed 500-mg tablet is a proportional scale-up of the approved 250-mg tablet. Pfizer noted that feedback from Biopharmaceutics and Chemistry was still pending from their proposal from March 10, 1999. There was an agreement to hold a teleconference on June 1 to review that proposal.

- A procedural discussion occurred regarding the regulatory filling plan with regard to user fee guidelines. There would be more than one NDA filed with one user fee. Pfizer would have to submit a total of 5 supplements as follows: two supplements to the suspension NDA and 3 supplements to the tablet NDA:

  NDA 50-710 Zithromax 200 mg/5ml Oral Suspension
  NDA 50-711 Zithromax 250 mg Tablets

- Dr. Moledina commented that she would like to see a side by side presentation of the safety data of 5-day azithromycin versus 3-day. Dr. Chikami stated that with regard to spontaneous adverse event reporting, it would be helpful to have an estimate of patient exposure, possibly by extrapolating from sales figures, in order to generate a denominator for the events seen in the spontaneous event database. A breakout by countries that have the approved 3-day and the 5-day regimen would be useful too.

- [illegible]

appropriate study reports that both include and exclude the three investigators who participated in trials trial that were felt to have lapses in GCP.

- Dr. Chikami indicated that in the proposal sent to the FDA on September 1998, it was discussed that a single robust — study would support — AECB indications. The information presented at this meeting have raised serious concern about the study, so at this time it is not clear if the single study is adequate to support — indications.

- Dr. Dunne stated that this application is based on the similarity of pharmacokinetics exposure between the 3-day and 5-day regimens. The safety and efficacy data are provided in support of the PK/PD argument.

- Dr. Albuerne (FDA) indicated to the sponsor should analyze the data based on gender, age, and race. Under the new FDAMA rules, failing to submit these information could result in a "refuse to file" the application.

- **Microbiology Issues:**

  1. For non-US clinical data:

     - The applicant should identified all the modifications and changes in those non-U.S. clinical studies that did not use susceptibility methodologies identical to the NCCLS susceptibility methods. All the modifications and changes should be justified

  2. The applicant should indicate whether the mechanism(s) of resistance of the non-U.S. clinical pathogens (is) are the same as those currently found in the U.S.

  3. The reviewer will look at the clinical bacteriological susceptibility results and evaluate whether the data correlates with the actual clinical outcome.

  4. Handouts provided to the sponsor

     - The Division provided a copy of "NDA HOLDERS LETTER" (January 26, 1993) and a copy of the criteria to be considered in constructing LIST #2 in the Microbiology subsection.

- Dr. Chikami explained to Pfizer that based on the information presented at this meeting raised several concerns regarding the proposed package for the 3-day dosing of Zithromax. These included:
    1. Dosing of the clinical studies
    2. The conduct of the studies
    3. The possible lack of availability of source data for some studies.

Unresolved issues or issues requiring further discussion:

- The 500-mg tablet proposal was raised. Pfizer noted that feedback was still pending from our proposal from March 10, 1999. There was an agreement to hold a teleconference on June 1, 1999 to review that proposal.

Action Items:

1. Pfizer will provide a comparison of safety profile for the3-day and 5- day regimens. This should include the post-marketing safety report from countries that have approval for both the 3-day and 5-day dosing regimens. An estimate of the total sales and total usage of the 3-day and 5-day dosing regimens should be included to provide a denominator for the-marketing reports.

2. —

    a. —

    b. —

    c. —

    d. —

    e. —

    f. —

3. The following information should be provided to DSI for reviews:

   a. Provide copies of the pivotal protocols and their respective blank or sample Case Report Forms for DSI review.

   b. Provide certified translations of the local country requirements (regulations) pertaining to study document retention and consent from human subjects in research.

   c. Provide the names and addresses of investigators who did not adhere to GCP.

   d. Provide a list of studies that were monitored versus those that were not.

   e. Provide a list of what source documents are available. FDA will review the pivotal protocols and Case Report Forms (when provided) and inform sponsor what essential source documents will be required to support the data.

4. Pfizer should include in reports for studies 92-004, F92-004, and 92-021, data with and without the data from sites that had problems with GCP compliance.

5. Identify and provide all the modifications and changes in those non-U.S. clinical studies that did not use susceptibility methodologies identical to the NCCLS susceptibility methods. Justify all the modifications and changes.

6. Indicate if the mechanism(s) of resistance of the non-U.S. clinical pathogens (is) are the same as those currently found in the U.S.

Minutes Prepared by: Jose R. Cintron, R.Ph., M.A.

Chair Concurrence: Gary Chikami, M.D.

Attachments/Handouts: Attendance sheet, Pfizer's overhead presentation

cc:
IND —
HFD-520/Div. Files
HFD-344/DSI/MThomas
HFD-520/Div.Dir/GChikami (S) 10/12/99
HFD-520/Medical Officer/NMoledina NM 6/30/99
HFD-520/ Microbiology Team Leader/ASheldon 7/1/99
HFD-520/Microbiology/HSilver HS 7/01/99
HFD-725/Biostatistics Team Leader/DLin DL 7/12/99
HFD-830/Chemistry/JTimper
HFD-880/ Team Leader Biopharmaceutics/FPelsor 7/1/99
HFD-520/ Project Manager/JCintron
HFD-520/AEvans

Concurrence Only:
HFD-520/CPMS/JBona 6/25/99
HFD-520/TLMO/MAlbuerne mda 7/13/99

Drafted by: jrc/May 20, 1999
Initialed by: JRC
Final:
File name: C:\\data\wordfiels\minutes\ — \aziMay13b

MEETING MINUTES

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pages of trade

secret and/or

confidential

commercial

information

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 50-784	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zithromax (azytrhomycin), 500 mg		Applicant: Pfizer Inc.	
RPM: Judit Milstein		HFD-520	Phone # 301-827-2207
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
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	May 24, 2002
❖ 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	( ) Verified (X) Not applicable
• 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).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Not Applicable
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Not available
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Not applicable
• 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)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Not applicable
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not applicable
• Applicant proposed	X
• Reviews	Not applicable
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Not applicable
• Documentation of discussions and/or agreements relating to post-marketing commitments	Not applicable
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Not applicable
❖ Memoranda and Telecons	Not applicable
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	April 12, 2000
• Pre-NDA meeting (indicate date)	May 13, 1999, and June 21, 2001(not available)
• Pre-Approval Safety Conference (indicate date; approvals only)	Not applicable
• Other (Guidance)	X

❖ Advisory Committee Meeting	
• Date of Meeting	Not applicable
• 48-hour alert	Not applicable
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	Not applicable
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	May 24, 2002
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	June 26, 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	May 21, 2002
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See clinical review, page 104
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Statistical review(s) *(indicate date for each review)*	May 17, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	May 13, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**X**
• Bioequivalence studies	Not applicable
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	May 3, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See chemist review
• Review & FONSI *(indicate date of review)*	See chemist review
• Review & Environmental Impact Statement *(indicate date of each review)*	See chemist review
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Not applicable
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable (see Page 44 of review) **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	May 15, 2002
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	Not applicable
❖ CAC/ECAC report	Not applicable

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

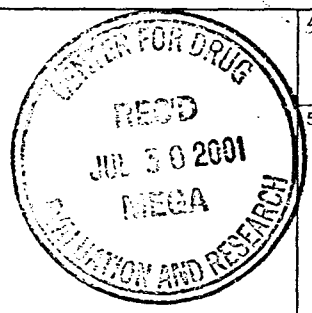
USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

Completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Pfizer Inc
50 Pequot Avenue
New London, CT 06320



2. TELEPHONE NUMBER *(Include Area Code)*

(860) 732-6991

3. PRODUCT NAME

Zithromax azithromycin Tablets 500 mg ®

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N050784 (N050670; N050710, N050711 by reference)

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

✗ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

N050710

(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4043

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ✗ NO

(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	John E. Wolleben Senior Vice President, Regulatory affairs	1 June 01

Created by: PSC Media Arts (301) 443-2454 EF

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 3/22/02	**DUE DATE:** 04/30/02	**ODS CONSULT #:** 01-0217-1

TO:
Janice Soreth, M.D.
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH:
Judith Milstein
Project Manager
HFD-520

PRODUCT NAME: Zithromax Tri-Pak (Azithromycin Tablet) 500 mg **NDA:** 50-784	**NDA SPONSOR:** Pfizer

SAFETY EVALUATOR: David Diwa, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name *Zithromax Tri-Pak* to determine the potential for confusion with approved proprietary and established names as well as pending drug names. DMETS has also reviewed blister pack labels and carton labeling, for possible interventions that may minimize medication errors.

DMETS RECOMMENDATION: DMETS does not recommend the use of "Tri-Pak" packaging configuration and nomenclature. In addition, we recommend implementation of labeling revisions contained in section III of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, R.Ph
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 480-8173

/S/

Jerry Phillips, R.Ph
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm 15B-032
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 26, 2002

NDA: 50-784

NAME OF DRUG: Zithromax Tri-Pak (Azithromycin Tablet) 500 mg

NDA HOLDER: Pfizer

I. INTRODUCTION

This consult is written in response to a March 22, 2002, request from the Division of Anti-infective Drug Products (HFD-520) to evaluate the proposed trade name *Zithromax Tri-Pak*, for a new 3-day regimen package of azithromycin.

The Division initially requested a review of the name [redacted] on July 27, 2001 (ODS consult 01-0217). The name *Z3Pak* was subsequently withdrawn after discussions between the Agency and the sponsor. The products listed below are currently approved under the proprietary name Zithromax (azithromycin):

Dosage Form	Strength	Application #	Approval Date
Oral Capsule	250 mg	50-670	November 1, 1991
Oral tablet	250 mg	50-711	June 12, 1996
Oral tablet	600 mg	50-730	July 18, 1996
Oral Suspension	100 mg/5 mL	50-710	October 19, 1995
Oral Suspension	200 mg/5 mL	50-710	October 19, 1995
Oral Suspension	1g/packet	50-693	September 28, 1994
Injection	500 mg/vial	50-733	January 30, 1997

In addition, the sponsor markets a 5-day dose package containing six 250 mg tablets under the proprietary name *Zithromax Z-Pak.*

PRODUCT INFORMATION

Zithromax Tri-Pak (Azithromycin) is a macrolide antibiotic indicated for the treatment of mild to moderate exacerbations of chronic obstructive pulmonary disease. It will be available in blister packs containing three 500 mg tablets. The recommended dose is one 500 mg tablet daily for 3 days.

II. RISK ASSESSMENT

This application was submitted for the addition of a 3-day dose package of azithromycin 500 mg tablets to the current azithromycin product line. The standard DMETS proprietary name review was not completed for this consult because the proprietary name *Zithromax* is already utilized in the marketplace.

A. EXPERT PANEL DISCUSSION

Expert opinion was gathered from DMETS Safety Evaluators regarding the safety of the proprietary name *Zithromax Tri-Pak*. Opinion was also sought from a representative of the Division of Drug Marketing, Advertising, and Communications (DDMAC) regarding promotional concerns over the proposed name. DDMAC expressed no concerns regarding promotional aspects of the name.

Overall, DMETS safety evaluators believed that the use of the term "*Tri*" in association with "*Pak*" could be misinterpreted as 3 packs and is therefore capable of causing medication dispensing errors. Some members believed that the name denotes a combination of three active ingredients. The safety evaluators also believed that while the letter "Z" contained in the name "*Z-Pak*" can be associated with Zithromax or azithromycin the term "*Tri*" contained in the proposed name bears no recognizable connection to either the established or the proprietary name.

Three names *Tritec, Trimpex* and *Prevpac* were identified as problematic in terms of the potential risk of name confusion with the modifier *Tri-Pak*. These product names are listed in Table 1 below, along with the dosage forms available and usual dosage.

TABLE 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Zithromax Tri-Pak	Azithromycin Tablets 500 mg	500 mg/day x3 days	
Tritec	Ranitidine Bismuth Citrate Tablets 400 mg	400 mg BID with Clarithromycin 500 mg TID	SA/LA
Trimpex	Trimethoprim Tablets 100 mg, 200 mg	4 mg/kg/day divided q 12 hrs in children 100 mg Q 12 hrs in adults	SA/LA
Prevpac	Lansoprazole Capsules, 30 mg Amoxicillin Capsules, 500 mg Clarithromycin Tablets, 500 mg	2 capsules of Lansoprazole/4 capsules of amoxicillin/2 tablets of clarithromycin BID x10 to 14 days	SA/LA
*Frequently used, not all–inclusive.		**LA: look-alike, SA-sound-alike.	

B. AERS and DQRS SEARCHES

The FDA Adverse Event Reporting System *(AERS)* database was searched for all post-marketing safety reports of medication errors reported for the active ingredient term "Azithromycin%" and for the trade name "Zithromax%", using the MedDRA Preferred Term, MEDICATION ERROR. This search strategy retrieved one hundred and forty-seven medication error reports, two of which were related to the misinterpretation of the

name Zithromax (see attachment A). The two reports pertained to the misinterpretation of *Zithromax* as *Biaxin* and *Zithromax Z-Pak* as *Zithromax 1 g pack.*

The Drug Quality Reporting System *(DQRS)* database was also searched for reports with the trade name "Zithromax" and the established name "azithromycin". We identified 20 medication error reports, 5 of which were errors involving the misinterpretation of Zithromax or azithromycin. Two reports pertained to the misinterpretation of *azithromycin* as *erythromycin.* A third report involved the misinterpretation of *Zovirax* injection as *Zithromax* injection while in a fourth medication error incident, *Z-Pak* was dispensed to a patient instead of *Pepcid.* The fifth report relates to an incident where a physician phone order for intravenous *Zinacef* was transcribed as intravenous *Zithromax.* The medication errors were reported between 1993 and 1998. Our data search did not uncover recent reports of medication errors involving the products identified.

C. SAFETY EVALUATORS RISK ASSESSMENT

DMETS does not recommend the use of the nomenclature "*Tri-Pak*" for the following reasons:

1. We note that *Tri-Pak* appears the most prominent on the labeling inferring that it is another proprietary name for the product and is therefore misleading.

2. Post-marketing experience with Zithromax *Z-Pak* indicates a tendency among drug prescribers to write for *Z-Pak* when ordering *Zithromax Z-Pak.* This leads us to believe that the proposed product will be prescribed as *Tri-Pak* rather than *Zithromax Tri-Pak.* Prescribing this product simply as *Tri-Pak* will be problematic in that it is not an approved proprietary name and will not be listed in drug reference texts. Practitioners unfamiliar with the name who attempt to find it in drug reference texts will be unsuccessful. This will create situations whereby some practitioners may default to a wrong product. Moreover, the name *Tri-Pak* bears striking look-alike qualities to the name *Z-Pak* when scripted (see writing sample on page 5). Although the names start with different letters and differ by 2 letters, such differences are not easy to distinguish when scripted. Since dosing directions are easily evident in the way the dose pack is designed prescribers will tend to leave out the dosing directions on prescriptions. This will render the name prone to confusion with *Z-Pak.* Patients who inadvertently receive a *Z-Pak* dosage pack instead of *Tri-Pak* will be deprived of the therapeutic benefit from the proposed formulation. In this case, the lower 250 mg 5-day regimen may provide subtherapeutic blood level concentration of azithromycin. Because *Tri-Pak* contains only a 3-day course of treatment, patients who inadvertently receive it may not get enough medication to complete the required 5 or 7 day course of therapy for other indications. This leads us to believe that the name *Z-Pak* and the proposed name *Tri-Pak* pose potential risk of causing medication errors, which will have an impact on treatment outcomes.

Tri-Pak

Take as dir

#1

Z-pak

Take as dir

#1

3. DMETS is concerned that the proposed packaging configuration which contains three 500 mg tablets may not be a reasonable packaging configuration. The 5-day course of therapy (Z-Pak) is approved for the majority of indications of use. The 3-day treatment regimen is approved for only one indication (mild to moderate exacerbations of chronic obstructive pulmonary disease). How will practitioners know which pack to dispense as most prescriptions are written "as directed" or "UD"?

4. The introduction of *Tri-Pak*, will add a third Zithromax packing configuration in which the label will either bear the phrase "*Pak*" or "*Packet*". Zithromax *Tri-Pak* contains three 500 mg tablets intended for a 3 day treatment of mild to moderate exacerbations of chronic obstructive pulmonary disease. Zithromax *Z-Pak*, is a 7-day dose pack containing 250 mg capsule dose-pack for a 5 day therapy (500 mg on the first day of treatment and 250 mg on days two through four). A third product, Zithromax oral suspension is available in a strength of 1g/*packet.* Zithromax oral suspension 1g/*packet* was confused with a prescription for *Z-Pak* (see attachment A). The proliferation of multiple names for one active ingredient, which contain common features in their nomenclature or strength, will heighten the risk of medication errors. We do not recommend the continuation of this proliferation of nomenclature associated with packaging configuration. If the Division allows such nomenclature then the sponsor should provide a unique name for the new packaging configuration of azithromycin in order to minimize the potential risk of medication errors.

   The panel also observed that when dosing directions are clearly evident on dose-packs prescribers tend to leave out the dosing directions and script "Use as directed" on prescription orders. Post-marketing experience with *Z-Pak* seems to follow this pattern. The dosing directions are evident in the manner in which *Zithromax Tri-Pak* is packaged. Three tablets are enclosed in blisters, each clearly marked with 1 of the 3 days. Therefore, prescribers will tend to leave out the dosing directions and script "Use as directed". This prescribing pattern will take away certain distinguishing factors such as the 500 mg strength and 3 day duration of therapy on a *Tri-Pak* prescription which may help differentiate it from a written prescription for other dose packs.

5. The DMETS Expert Panel also believed that three approved proprietary drug names *Tritec, Trimpex* and *Prevpac* pose the potential risk of name confusion with the modifier *Tri-Pak.*

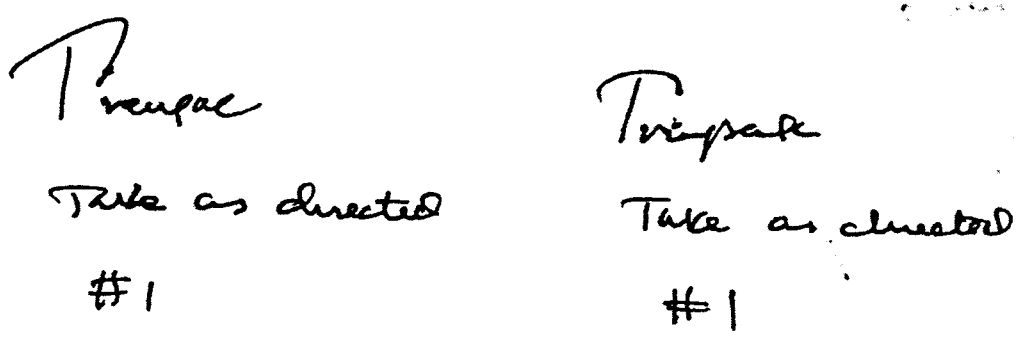
   The Expert Panel was concerned about the potential risk of committing dispensing errors if *Tri-Pak* is misinterpreted as 3 packs. The prefix "*Tri*" is used in many drug names including antibiotic products in the same therapeutic class as azithromycin. An example is *Trimox,* a proprietary for the antibiotic amoxicillin. Similarly, there are approved drug names in which the prefix "*Tri*" is linked to the suffix with a hyphen as has been proposed. Such names include *Tri-Tannate* (Chlorpheniramine, Pyrilamine, Phenylepherine), *Tri-Cyclen* (Ethinyl Estradiol, Norgestimate), *Tri-Norinyl* (Ethinyl Estradiol, Norethindrone) *Tri-Leven* (Levonorgestrel, Ethinyl Estradiol) and *Tri-Immunol* (Diphthera and Tetnus taxoids, pertussis vaccine), *Tri-Nasal* (Triamcinolone Nasal Spray). It appears that in most cases these are products containing more than one active ingredient. In the case of *Tri-Nasal*, the prefix "*Tri*" denotes part the established or active ingredient name, Triamcinolone while the suffix denotes the route of administration. The proprietary name *Trimox* retains the part of the established name amoxicillin. Part of our concern is that in many cases the modifier "*Tri-Pak*" will be used as a stand-alone name on prescriptions rather than in association with Zithromax. The prefix "*Tri*" and the suffix "*Pak*" have no relationship to the number of active ingredients contained in the product, the established name or route of drug administration. There is some risk that people may misinterpret "*Tri*" as the number three, which will lead to dispensing errors.

   Although *Tritec* (ranitidine bismuth citrate) was identified as a drug name that could be confused with Tri-Pak, there is no overwhelming data in support of this observation based on information currently available. *Tritec* is an H_2 antagonist indicated for the treatment of active duodenal ulcers associated with *H. pylori* when used in combination with clarithromycin. The recommended dose is 400 mg twice daily for 4 weeks taken with clarithromycin 500 mg two times daily for the first 2 weeks. Overall, there are risk factors that can cause the name *Tritec* to be confused with *Zithromax Tri-Pak*, when simply written as *Tri-Pak.* The name *Tritec* and *Tri-Pak* each contain 6 letters and share the prefix "*Tri*". However, *Tritec* is usually prescribed for use with clarithromycin for the treatment *H. pylori.* Clarithromycin a macrilide antibiotic is in the same class as azithromycin. Therefore, a prescription order for *Tri-pak* (azithromycin) and clarithromycin will likely be flagged as duplicative therapy because the two drugs are pharmacologically similar. Moreover, the duration of therapy with *Tri-Pak* is 3 days while *Tritec* is 4 weeks. Additionally, Tritec is administered twice daily while Tri-Pak will be administered once daily. Furthermore, Tritec is available in 400 mg tablets while Tri-Pak will contain 500 mg tablets. Because *Tritec* is part of an *H. pylori* treatment regimen, the potential risk of confusing it with *Tri-Pak* minimal.

   Trimpex (trimethoprim) is used in the treatment of urinary tract infections, acute otitis media in children and acute exacerbations of chronic bronchitis. It is also used in combination with other agents in the treatment of *pneumocystis carnii pneumonia.* The usual dose of *Trimpex* is 4 mg/kg/day in children and 100 mg every 12 hours or 200 mg every 24 hours in adults. The product is available in 100 mg and 200 mg oral

tablets. The name *Tri-Pak* and *Trimpex* share the prefix "*Tri*", both contain the letter "*p*" and are similar in sound and script. However, a prescription for *Trimpex* will indicate the tablet strength for appropriate dispensing since it is available in multiple strength. Moreover, the dosing regimen and average duration of therapy with *Trimpex* is different from *Zithromax Tri-Pak*. Therefore the potential risk of name confusion between *Trimpex* and *Tri-Pak* based on information currently available appears to be minimal.

Prevpac (lansoprazole/amoxicillin/clarithromycin) is combination of the proton pump inhibitor Lansoprazole and two antibiotics, amoxicillin and clarithromycin. It is used in the treatment of active duodenal ulcers associated with *H. pylori*. *Prevpac* is available in blister packs containing twenty-eight 30 mg capsules of lansoprazole, forty-eight 500 mg capsules of amoxicillin and twenty-eight 500 mg tablets of clarithromycin. The recommended dose is 30 mg of lansoprazole, 1 gm of amoxicillin and 500 mg of clarithromycin twice daily for 10 to 14 days. Because *Prevpac* is provided in a convenience dose package where the dosing directions are clearly evident, prescribers usually leave out the complete dosing instructions on prescriptions. Moreover, writing out the dose and complete directions will be cumbersome for a 3-drug combination. This practice will render prescriptions for *Prevpac* and *Tri-Pak* prone to misinterpretation since they will be difficult to distinguish (see writing sample on page below).



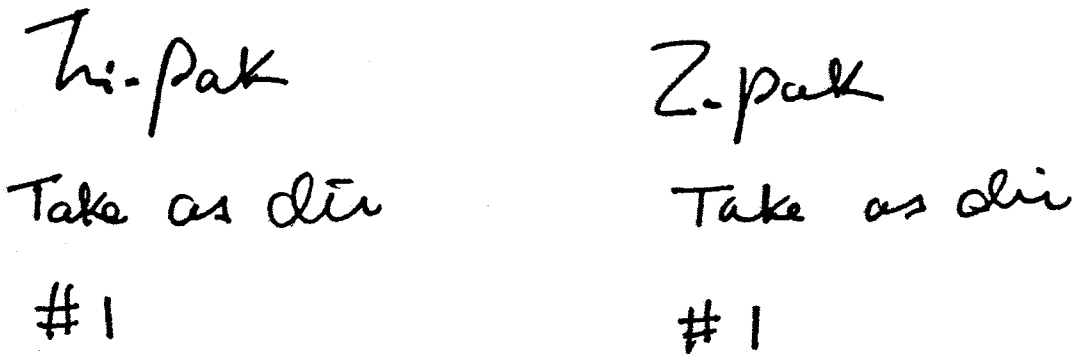
III. COMMENTS TO THE SPONSOR

DMETS does not recommend utilizing a name for the packaging configuration for the reasons listed below. Additionally, in reviewing the name *Zithromax Tri-Pak*, we have identified look-alike and sound-alike similarities between the proposed name, and the approved products *PrevPac* and *Zithromax Z-Pak* that pose potential risk of causing drug name confusion.

1. We note that *Tri-Pak* appears the most prominent on the labeling inferring that it is another proprietary name for the product and is therefore misleading.

2. Post-marketing experience with Zithromax *Z-Pak* indicates a tendency among drug prescribers to write for *Z-Pak* when ordering *Zithromax Z-Pak*. This leads us to believe that the proposed product will be prescribed as *Tri-Pak* rather than *Zithromax Tri-Pak*. Prescribing this product simply as *Tri-Pak* will be problematic in that it is

not an approved proprietary name and will not be listed in drug reference texts. Practitioners unfamiliar with the name who attempt to find it in drug reference texts will be unsuccessful. This will create situations whereby some practitioners may default to a wrong product. Moreover, the name *Tri-Pak* bears striking look-alike qualities to the name *Z-Pak* when scripted (see writing sample below). Although the names start with different letters and differ by 2 letters, such differences are not easy to distinguish when scripted. Since dosing directions are easily evident in the way the dose pack is designed prescribers will tend to leave out the dosing directions on prescriptions. This will render the name prone to confusion with *Z-Pak*. Patients who inadvertently receive a *Z-Pak* dosage pack instead of *Tri-Pak* will be deprived of the therapeutic benefit from the proposed formulation. In this case, the lower 250 mg 5-day regimen may provide subtherapeutic blood level concentration of azithromycin. Because *Tri-Pak* contains only a 3-day course of treatment, patients who inadvertently receive it may not get enough medication to complete the required 5 or 7 day course of therapy for other indications. This leads us to believe that the name *Z-Pak* and the proposed name *Tri-Pak* pose potential risk of causing medication errors, which will have an impact on treatment outcomes.



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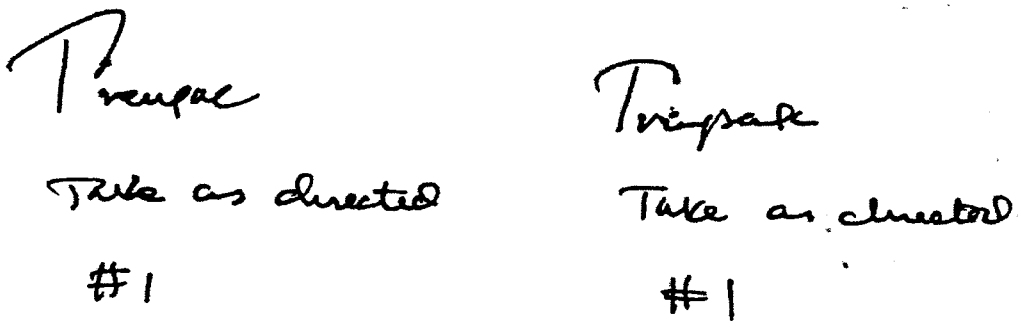

DMETS also reviewed the proposed professional blister pack label and carton labeling for *Zithromax Tri-Pak*, and has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. BLISTER PACK CONTAINER LABEL (Professional Sample)

1. The use of the logo "*Z*" which prominently appears on the label heightens the risk of confusing the product with *Z-Pak*.

2. Provide an "Rx only" statement on the principal display panel".

3. The statements "A full course of antibiotic therapy in just 3 doses" should be deleted or relocated to the package insert as it is promotional in tone.

4. Delete the statement "Zithromax keeps on working days 4-10".

5. The DOSAGE AND USE, RECOMMENDED STORAGE and strength identity statements are not legible. Increase the prominence and clarity of the statements.

6. Label the blister pack such that day 1 is at the top and each tablet blister is provided with a strength identity or include an "Each tablet contains..." statement. This will clearly identify the tablet strength in cases where part of the dose-pack container has been torn off.

IV. RECOMMENDATIONS

A. DMETS does not recommend the use of "Tri-Pak" packaging configuration and nomenclature.

B. We recommend implementation of the labeling revisions as outlined in Section III of the review to minimize potential errors with the use of this product.

We would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph. at 301-827-3242.

/S/

David Diwa, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

ATTACHMENT A

(The following narratives are summaries of medication error reports transcribed from ARES data. Dates provide the times reports were received by the Agency)

#	AERS/DQRS/US PREPORT #	DATE	TYPE OF RPT/ERROR	ABBREVIATED NARRETIVE
1	3179694-7	Jan-12-99	Written prescription Actual error	A technician entered Zithromax prescription as Biaxin 250 mg. The prescription order was for 4 tablets of Zithromax to be taken at one time for the treatment of clamydial infection. The pharmacist filled the prescription by only checking the label against the stock bottle.
2	3601344-3	Oct-26-00	Written prescription Actual error	A written prescription for Zithromax Z-Pak was filled with Zithromax 1 g pack. The directions for Z-pak were typed on the label. The error was caught and corrected.
3	M122449	Unspecified	Phone prescription Actual error	Erythromycin was given instead of Azithromycin – sounded too similar.
4	U000362	Unspecified	Unspecified Actual error	A physician ordered "Azithromycin 500 mg IVPB now and 250 mg IV daily" and a nurse administered "Erythromycin" to the patient.
5	U050822	Unspecified	Unspecified Actual error	A pharmacy technician mixed Zovirax 500 mg IVPB instead of Zithromax 500 mg IVPB. A pharmacist caught the error and the patient received the proper medication. This was one of two errors by different technicians in one month.
6	U080908	Unspecified	Unspecified Actual error	Z-Pak was dispensed instead of Pepcid. Wrong patient-wrong drug.
7	U041320	Unspecified	Phoned prescription Actual error	A physician telephone order for Zinacef 750 mg every 8 hours was transcribed as Zithromax 750 mg IV every 8 hours.

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

/s/

David Diwa
4/29/02 03:06:19 PM
PHARMACIST

Alina Mahmud
4/29/02 03:10:09 PM
PHARMACIST

Carol Holquist
4/30/02 08:19:27 AM
PHARMACIST

Jerry Phillips
5/6/02 08:38:21 AM

7 pages redacted from this section of the approval package consisted of draft labeling