CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 050733

Trade Name : ZITHROMAX INJECTION

Generic Name: Azithromycin for intraveneous injection

Sponsor : Pfizer, Inc.

Approval Date: January 30, 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-733

JAN 30 1997

Pfizer, Inc
Attention: Mr. Robert B. Clark
Senior Associate Director
235 East 42nd Street
New York, N.Y. 10017-5755

Dear Mr Clark:

Please refer to your new drug application dated February 6, 1996, received February 8, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Zithromax® (azithromycin for intravenous injection).

We acknowledge receipt of your submissions dated May 31, 1996, August 20, 1996, and October 30, 1996. The User Fee goal date for this application is February 6, 1996.

This new drug application provides for the treatment of patients with Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus,* or *Streptococcus pneumoniae;* and Pelvic inflammatory disease due to *Chlamydia trachomatis, Mycoplasma hominis,* or *Neisseria gonorrhoeae* in patients who require initial intravenous therapy.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated January 30, 1997. This labeling was agreed to at the meeting held today, January 30, 1997, between representatives from the Division of Anti-Infective Drug Products and Pfizer, Inc. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on January 30, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-733. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Jose R. Cintron, R.Ph., M.A., Project Manager, at (301) 827-2125.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-733-
HFD-520/Div. files
HFD-002/ORM (with labeling)
HFD-2/M.Lumpkin
HFI-20/Press Office (with labeling)
HFD-104/TNearing
HFD-101/L.Carter (with labeling)
HFD-830/CCHEN
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-021/J.Treacy (with labeling)
HFD-~~426~~/BIOPHARM/HSun HFD-880
HFD-520/MO/LGirardi 1/30/97
HFD-520/CHEM/JTimper
HFD-520/PHARM/MAdeyemo
HFD-520/MICRO/HSilver HVS (1/30/97)
HFD-520/labeling File/CDeBellas
HFD-520/PMS/JCintron
HFD-725/STAT/SBell
TEAM LEADERS
HFD-~~426~~/TLBIOPHARM/FPelsor HFD-880
HFD-520/TLMO/MAlbuerne
HFD-520/Act.TLCHEM/DKatague
HFD-520/TLPHARM/ROsterberg
HFD-520/TLMICRO/ASheldon 1/30/97
HFD-725/TLSTAT/DLin
HFD-725/Div.Dir/RHarkins

Drafted by: jrc/January 17, 1997/
Initialed by:
final:

APPROVAL (AP)

Concurrence Only:
HFD-520/TLMO/MAlbuerne mda 1/30/97
HFD-520/CPMS/JBona 1/29/97
HFD-520/Act.Dir/DFeigal

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-733 Supplement # ____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Zithromax (azithromycin IV) Action: AP AE NA

Applicant Pfizer Therapeutic Class Macrolide

Indication(s) previously approved Adult: community-acquired pneumonia (CAP) or pelvic inflamatory disease (PID) who require initial intravenous antibiotic therapy.

Pediatric information in labeling of approved indication(s) is adequate ____ inadequate XX

Indication in this application Community Adquired pneumonia due to Chlamydia pneumoniae and Mycoplasma pneumonieae (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. **If none of the above apply,** attach an explanation, as necessary. **Safety and effectiveness in pediatric patients have not been established.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Jose R. Cintron, R.Ph., M.A. — Signature of Preparer and Title

January 07, 1997 — Date

cc: Orig NDA/PLA/PMA # 50-733
HFD-520/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 1/24/97)

Joint Review by Medical Officer and Statistician of NDA 50-733

I. General Information

Name of Drug: Zithromax® (Azithromycin for Intravenous Injection)

Pharmacologic Category: Antibiotic

Applicant: Pfizer, Inc.
235 East 42 Street
New York, NY 10017-5755
(212) 573 3412

Date of Submission: February 5, 1996
Received in CDER: February 6, 1996
Date Assigned: March 8, 1996
Date Reassigned: June 1, 1996
Date Review Begun: July 5, 1996
Date Review Completed: January 27, 1997
Medical Officer: Gino Girardi, M.D., HFD-520
Statistical Reviewer: B. Sue Bell, Ph.D., HFD-725
Project Manager: Jose Cintron, HFD-520

Related IND's:
Related NDA's: 50-670, 50-693, 50-710

Proposed Indications:

The sponsor seeks approval for intravenous azithromycin (followed by oral therapy) in the treatment of:

Proposed Dosage and Administration:

Regulatory Background

Zithromax (azithromycin) Capsules have been approved previously for use in the treatment of respiratory tract infections, skin and skin structure infections and *Chlamydia trachomatis* genitourinary infections in patients 16 years of age and older (NDA 50-670, approved November 1, 1991). NDA 50-693 was approved September 28, 1994, which provided for a single 1 gram dose packet. On October 19, 1995, Zithromax for oral suspension (NDA 50-710) was approved for the treatment of acute otitis media and streptococcal pharyngitis/tonsillitis in pediatric patients. On November 22, 1996, Zithromax capsules were approved for treating cervicitis and urethritis due to *N. gonorrhoeae*, genital ulcer disease (chancroid) due to *H.ducreyi*. On December 20, 1996, Zithromax oral suspension (NDA 50-710/S-001) was approved for treatment of pediatric patients with mild to moderate community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus inflluenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae.* Zithromax capsules were also approved on the same day for treatment of adult patients with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (NDA 50-670/S-010).

Materials Reviewed

--Clinically related material from volumes 1.1, 1.2, and 1.25-1.83 were reviewed.
--Electronic submission of data provided in SAS format was received September 16, 1996.

II. Table of Contents

III. Chemistry/Manufacturing and Controls

See review by Dr. Timper (Also see page 50 of this review for comments on solubility).

IV. Animal Pharmacology/Toxicology

The sponsor conducted seven pre-clinical studies to support the use of intravenous azithromycin in humans. Two 2-week studies in rats and dogs, one-month studies in rats and dogs, and an *in vitro* hemolysis/compatibility and a rabbit intravenous irritation study were performed. The 2-week and one-month studies had doses of up to 20/mg/kg/day. Analysis of blood and tissue, liver and spleen indicated dose-related concentrations of azithromycin. Concentrations in liver and spleen were higher than those observed in blood. Lysosomal lamellar bodies, referred to as phospholipidosis, were observed in the bile duct, gall bladder, and mesenteric lymph nodes of the dogs and in the bile ducts of the rats at doses of 10 and 20 mg/kg. Phosholipidosis has also been observed in oral studies with animals. The significance of this in humans is not known.

Conclusions of the pharmacology/toxicology review state that the results of the animal studies were consistent with those previously reported following oral administration of azithromycin in dogs and rats. No unique toxicity seems associated with the intravenous administration of azithromycin in these species. For complete information, please see Dr. Adeyemo's review dated 6/20/96.

V. Microbiology

Please see Microbiology review.

VI. Human Pharmacokinetics/Pharmacodynamics

Following oral administration as capsules, azithromycin is rapidly absorbed and widely distributed throughout the body. The bioavailability of an oral dose of 500 mg azithromycin relative to the 500 mg intravenous solution infused over 20 minutes is 37% (mean AUC-72: 3.39 for capsule dose versus 9.1 μg·h/mL, respectively). Ten studies, two of which were pivotal, were conducted to evaluate the pharmacokinetics and/or toleration of intravenously administered azithromycin in adult subjects or patients. The studies utilized daily azithromycin IV doses of 500 mg for 2 to 5 days and either infusion concentration and duration of 2mg/mL over 1 hour or 1mg/mL over 3 hours. These dosage regimens are identical to those used in the pivotal adult IV efficacy/safety studies in hospitalized patients with community-acquired pneumonia and in

pelvic inflammatory disease. Of note, the mean disposition half-life following intravenous dosing in healthy volunteers ranged from 65 to 72 hours.

VII. Clinical Studies

Introduction and Overview

The sponsor submitted this application to support the safety and efficacy of 2-5 doses of azithromycin (500 mg) by the intravenous route, followed by 500 mg/day orally for up to 10 days of therapy for CAP. For PID, the sponsor seeks approval for one or two doses of azithromycin (500 mg) by the intravenous route, followed by 250mg/ day orally for a total of up to 7 days of therapy.

Five open studies were conducted to evaluate azithromycin for treatment of CAP, all of which employed initial therapy with the intravenous formulation of azithromycin at 500 mg/day for 2 to 5 days, followed by 500 mg/day by the oral route for a total of 7 to 10 days of therapy. Two pivotal studies were conducted in the United States; study 93CE33-0618 compared azithromycin in a 1:1 randomization with cefuroxime (2250 mg/day IV followed by 1000 mg/day PO), with or without erythromycin (up to 2 g/day by any route). Study 93CE33-0625 was a non-comparative study in which the primary measures of efficacy were the clinical and bacteriological outcomes by pathogen. A total of 414 patients received azithromycin for CAP in the pivotal United States studies.

Three supportive studies of azithromycin monotherapy for CAP were conducted in other countries. Two studies were comparative. Studies 066-350 and 066-349 evaluated azithromycin versus cefuroxime with or without erythromycin, and versus penicillin followed by oral amoxicillin with or without erythromycin. Study 066-359 was non-comparative. A total of 289 patients received azithromycin for CAP in these studies and 278 were included in an intent-to-treat analysis at end-of-treatment..

Two pivotal studies of IV/PO azithromycin for treatment of PID were conducted in other countries (066-341 and 066-342). Both studies employed three treatment groups; one group received azithromycin alone (one IV dose of 500 mg followed by 250 mg/day orally for six days or two doses IV followed by 250 mg/day orally for five days). A second group received the same course of azithromycin in conjunction with metronidazole (given IV for one or two days followed by oral dosing for a total of 12 days or solely by the oral route at 1200 mg/day for all 12 days). The third group received a comparative regimen (either doxycycline 200 mg/day for 21 days plus amoxicillin-clavulanate at 3g/day IV for 5 days followed by 1500 mg/day PO for 16 days or a single dose of 2 g cefoxitin with probenicid on day one plus docycycline 200 mg/day PO for 14 days plus oral metronidazole as above).

Indication #1; Community Acquired Pneumonia (CAP)

Pivotal Studies (United States): Protocols 93CE33-0618 and 93CE33-0625

Protocol 93CE33-0618:

AZITHROMYCIN IN THE TREATMENT OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA. A MULTICENTER OPEN COMPARATIVE TRIAL EMPLOYING CEFUROXIME AS A COMPARATIVE AGENT.

Thirty-seven centers in the United States participated in this study.

Study Dates: 24 Nov 93 - 28 May 95

Study Objective: To compare the safety and efficacy of azithromycin and cefuroxime against susceptible pathogens in the treatment of hospitalized patients with community acquired pneumonia (CAP).

Methods

Study Design: This study was conducted as a multicenter, parallel group, randomized, open-label, comparative trial of azithromycin versus cefuroxime. Patients were to be evaluated at baseline, daily during hospitalization, on Day 3 of therapy, every 5 to 7 days during therapy, 10 to 14 days post therapy, and 4 to 6 weeks post therapy.

Inclusion Criteria:

- Age at least 16 years
- Women of childbearing potential should have had a negative urine pregnancy test
- Patients must have required hospitalization
- Clinically and radiographically/microbiologically documented CAP
- Informed written consent

Exclusion Criteria:

- Pregnant or lactating women
- Known hypersensitivity or intolerance to beta-lactam or macrolide antibiotics
- Patients with active peptic ulcers, gastrectomy, or other conditions affecting drug absorption
- Evidence or history of significant hematological, renal, cardiovascular, or hepatic disease, AIDS, HIV infection, or metastatic tumor. This includes the following concomitant medical conditions:
    a. Leukopenia (absolute neutrophil count < 1,000/cu.mm); thrombocytopenia

(platelet count < 75,000/cu.mm); anemia (Hgb < 9g/dL); or known bleeding disorder.

b. Creatinine clearance < 25 mL/min

c. Alkaline phosphatase > 2 times the laboratory range upper limit of normal; AST(SGOT) or ALT(SGPT) > 2 times the laboratory upper limit of normal; or, total bilirubin > 1.5 mg/dL.

- Patients receiving chemo or immunosuppressive therapy.
- Known drug or alcohol dependence.
- Presence of infection that may have required treatment with an antibiotic other than the study drugs.
- Treatment with any other potentially effective antibiotic within 24 hours prior to enrollment.
- Treatment with another investigational drug within four (4) weeks prior to enrollment, or previous enrollment in this protocol.
- Chronic bronchitis, bronchiectasis, or chronic obstructive pulmonary disease (COPD) in the absence of an acute pneumonia.
- Evidence of any of the following:

  a. Predominance of Gram negative rod other than *Haemophilus* on sputum Gram's stain. Slides must have been read prior to randomization of the patient.

  b. Signs and symptoms suggestive of infection with a Gram negative organism other than *Haemophilus.*

  c. Aspiration pneumonia

  d. Postobstructive pneumonia
- Suspected septic shock characterized by fever and systolic blood pressure < 90 mm Hg or mean arterial pressure < 70 mm Hg.
- Rapidly progressive underlying disease that precludes evaluation of therapy.
- Presence of coma or requirement for endotracheal intubation.
- Use within the past 14 days prior to study enrollment, or concomitant use of terfenadine or loratidine. Also use within the past 30 days prior to study enrollment, or concomitant use of astemizole.

MO Comment: These criteria are consistent with the 1992 Guidelines for the Evaluation of Anti-infective Drug Products.

Minimal Diagnostic Criteria

1. Clinical Criteria: Evidence of acute infection with at least one of the following:

   a. Any chest findings suggestive of bacterial pneumonia (chest pain, cough, rales, bronchi, and/or signs of consolidation)

   b. Oral temperature > 38 degrees Centigrade

c. Leukocytosis (WBC > 10,000/cubic mm or > 15% band forms)

Eligible patients must have met clinical criteria. In addition, they must also have met radiographic or confirmed microbiologic data OR radiographic and confirmed microbiologic data.

2. Microbiologic and other etiologic (non-culture) criteria: Specimens obtained by expectoration or by endotracheal aspiration were to be screened microscopically for suitability of culture (presence of > 10 polymorphonuclear leukocytes and < 25 squamous epithelial cells per low power field of a Gram stain specimen. These specimens were to be cultured in appropriate media at each investigator's local laboratory. These specimens were also to be sent to designated reference laboratories for *Mycoplasma* and *Legionella* cultures. Two sets of blood cultures were to be drawn on all patients and pleural fluid, if present, should have been aspirated and examined by microscopy and cultured for aerobes and anaerobes. The microbiologic diagnosis of infectious pneumonia was to be confirmed by the following criteria:

a. Purulent sputum and identification of a predominant pathogen by culture. A baseline respiratory sample must have been obtained. When an acceptable sputum sample could not be obtained at the baseline visit because the patient was dehydrated, the patient could still have entered the study. Following rehydration, an acceptable sputum sample must have been obtained no later than 24 hours following the first dose of intravenous drug. If a sputum sample could not have been obtained at the baseline visit because of possible infection with an atypical pathogen, patient entry into the study should have been considered on a case by case basis.

MO Comment: This is an important consideration in determining the evaluability of each patient. A patient will be deemed clinically evaluable provided the clinical and radiographic criteria support a diagnosis of pneumonia. In the absence of a distinct pathogen, patients may be clinically evaluable, but not microbiologically evaluable, provided no other diagnosis is likely, such as congestive heart failure.

Material from endotracheal suctioning could also have been used. Slides should have been saved and made available as part of the case record; or

b. Transtracheal aspirate, bronchial brushings, or biopsy material which on Gram's stain revealed neutrophils, and a predominant suspect pathogen by smear or culture; or

c. Pleural fluid or direct lung aspirate, with identification of a predominant pathogen on Gram's stain or by culture; or

d. Positive blood culture yielding a pathogen in a patient with a compatible clinical syndrome of bacterial pneumonia and in the absence of another source of bacteremia.

Isolated organisms must have been susceptible to the assigned study drug by standard disk diffusion and broth dilution method. Clinical improvement or stabilization must have been documented by 72 hours to permit retention in the study.

MO Comment: Patients will be graded as clinical failures if removed from the study because of deteriorating clinical status.

Detection of antigen specific DNA by non-culture methods may have been used as surrogate markers for supportive evidence of infection.

Isolation by culture was not required for the diagnosis of *Mycoplasma pneumoniae, Legionella pneumophila, or Chlamydia pneumoniae.* Serum for these pathogens will have been drawn at baseline and at 4-6 weeks following completion of therapy.

3. Radiographic Criteria: New pulmonary infiltrate(s) on chest x-ray within 48 hours of institution of therapy, which could be attributed to some other etiology.

MO Comment: These criteria are consistent with the 1992 Guidelines for the Evaluation of Anti-infective Drug Products.

B. Concomitant Therapy

During the study the patient may not have been treated with another antibiotic active against the pathogen(s) under study. If other anti-infective medication was required, treatment with study drug should have been discontinued.

MO Comment: Patients who required additional or other antimicrobial therapy will be failures.

C. Drug Administration

Patients were to be randomized to

1. Azithromycin, 500 mg IV in 500 mL of normal saline over three hours qd for 2 to 5 days (minimum of two doses) depending on the patients clinical response, followed by azithromycin capsules 500 mg orally qd to complete a total of 7 to 10 days of therapy. For patients suspected of having infection due to *Mycoplasma pneumoniae, Legionella pneumophila, or Chlamydia pneumoniae,* no additional antibiotic therapy would have been needed.

Or

2. Cefuroxime, 750mg IV q8h for 2 to 7 days (minimum of 6 doses), depending on the patients clinical response, followed by cefuroxime axetil 500 mg PO q 12h to complete a total of 7 to 10 days of therapy. For patients suspected of having infection due to *Mycoplasma pneumoniae, Legionella pneumophila, or Chlamydia pneumoniae,* erythromycin 500 mg PO qid (or 500 mg to 1 g IV q6h for seriously ill patients) may have been added and continued for up to 21 days. -

Efficacy

A. Clinical

Clinical response was to be classified by the investigator as cure, improvement, or failure. The clinical evaluation was to be based on resolution or improvement of clinical and laboratory signs of infection such as defervescence, reduction of leukocytosis, disappearance or diminution in purulent sputum production, stabilization in general physical condition, and radiographic resolution of lung infiltrates. Patients were to have been assessed at baseline, day 3, and every 5 to7 days thereafter during therapy and 10 to 14 days and 4 to 6 weeks after treatment was completed.

Arterial blood gas determinations and pulse oximeter readings were to have been performed as clinically indicated. Chest x-ray was to be obtained at baseline, 3 days after starting therapy, 10 to 14 days and 4 to 6 weeks following completion of therapy. Whenever possible, the same radiologist from the same institution should have interpreted all radiographs.

B. Laboratory

Cultures of respiratory tract secretions were to be done at baseline, and, if obtainable, at Day 3, every 5 to 7 days during treatment, 10 to 14 days post-therapy, and 4 to 6 weeks post-therapy, as well as when clinically indicated. Only "adequate" sputum specimens as previously defined were to be cultured.

Culture, identification, and susceptibilities of *Legionella* spp., and *Mycoplasma pneumoniae* to azithromycin were determined at the reference laboratories of

Clinical laboratory identification of *Legionella* was accomplished by isolation of the organisms from clinical specimens. Confirmation of the identity of *Legionella* was accomplished using a direct fluorescent antibody test for *L. pneumophila* and by serotyping methodologies for other species. Susceptibility testing of *Legionella* was performed by broth dilution determination of MICs. Confirmation of the identity of *Mycoplasma pneumoniae was accomplished* using a polymerase chain reaction (PCR) technique. Susceptibility testing of *M. pneumoniae* was performed by broth dilution determination of MICs.

Serologic Testing for *Chlamydia, Mycoplasma,* and *Legionella*:
Pneumonia: Microimmunofluorescence (MIF) testing for the detection of antibody to *Chlamydia pneumoniae* was conducted at the laboratory of

In this serological test, an indirect fluorescent antibody technique was adapted such that diluted sera were tested against different Chlamydial antigens. Antibody, in terms of specific immunoglobulin class, was assessed in this system using commercially available fluorescein-conjugated anti-human specific immunoglobulin (IgM, IgG or IgA).

Enzyme-linked immunoabsorbent assay (ELISA) testing for antibody to *Mycoplasma pneumoniae* was conducted at the laboratory of

Titers of sera from healthy laboratory personnel were used to establish a cutoff point of less than 10 as negative results for both IgM and IgG. IgM titers $\geq$ 10 are considered to represent strong evidence of an acute infection in this test system. IgG titers 10 or greater without corresponding elevation of IgM antibody may indicate past infection. A fourfold increase in IgG titer was considered clinically significant.

Legionella pneumophila indirect fluorescent antibody test (IFA) for antibody to *Legionella pneumophila* was conducted at the laboratory of

A fourfold rise in titer from the acute to the convalescent phase was considered to provide evidence of a recent infection for *Legionella pneumophila* serogroup 1.

Bacteriological Response

The bacteriological response was to be classified by the sponsor for each pre-treatment causative pathogen for each patient according to post-baseline bacteriological results and the last recorded clinical outcome as follows:

1. Eradication: Elimination of the original causative organism(s) from the same site (e.g., expectorated sputum, pleural fluid, or blood) during or upon completion of therapy.

2. Presumed eradication: Absence of appropriate culture material for evaluation because the patient was clinically improved and there was no more sputum production, or repeat aspiration of pleural fluid was no longer justified.

3. Persistence: Failure to eradicate the original causative organism(s) from sites previously listed, whether signs of inflammation were present or not.

4. Presumed Persistence: No sample was taken at the time alternative treatment was instituted, and the patient was considered a clinical failure.

5. Superinfection: Development of a new lower respiratory tract infection (documented by fever, radiography, and/or auscultatory findings) during treatment or within 3 days posttreatment, due to a new or resistant pathogen which was not recognized as the original causative organism(s).

Definition of the Comparator Group

The study protocol allowed the addition of erythromycin to cefuroxime when atypical pathogens were suspected. The study was not designed to make a separate comparison to cefuroxime plus erythromycin. It was not expected that clinical response would be different between the

subgroup of patients who were treated with cefuroxime plus erythromycin compared to those who received only cefuroxime. Therefore, the study randomization was not stratified to account for this variable.

MO Comment: Outcomes at the 10-14 day post-therapy visit and at the 4-6 week follow-up visit were compared. Clinical cure rates were the primary endpoint. . Evaluability was based on each patient meeting the sponsor's criteria. In addition , the investigator's comments from the case report forms were reviewed to aid in determining patient evaluability.

Sponsor's Efficacy Results

Patient Disposition (Total)

Evaluation Groups	Azithromycin n (%)	Comparator n (%)
Randomized	206 (100)	207 (100)
Received Study Medication	202 (98)	201 (97)
Included in ITT Analysis		
For 10-14 Day Visit	163 (79)	159 (77)
For 4-6 Week Visit	150 (73)	146 (71)
Included in Clinically Evaluable Analysis		
For 10-14 Day Visit	137 (67)	131 (63)
For 4-6 Week Visit	130 (63)	122 (59)
Total Clinically Evaluable for either visit	150 (73)	141 (68)
Number of Patients with a Baseline Pathogen	81 (39)	89 (43)
Evaluable for Bacteriological Outcome	53 (26)	44 (21)
Analyzed for Adverse Events	202 (98)	201 (97)
Analyzed for Laboratory Data	202 (98)	201 (97)

Thirty-seven centers were originally recruited to participate in the study. Thirty-six centers ultimately enrolled patients.

Number of Patients in Azithromycin Group

Center Number (Investigator, City)	Randomized	Received Treatment	Clinically Evaluable	Bacteriologically Evaluable
116 (Richard Greenberg MD, Lexington, KY)	18	17	16	9
107 (Guy Amsden, Pharm. D., Worcester, MA)	4	4	2	1
108 (Jack Bernstein MD, Dayton, Ohio)	1	1	1	0
237 (JF Foss, MD, Shreveport, LA)	5	5	3	0
111 (Naresh Dewan, MD, Omaha, NE)	3	3	2	1
112 (Charles Ericcson MD, Houston, TX)	4	4	1	0
113 (James Felicetta MD, Phoenix, AZ)	11	11	6	1
114 (Mitchell Fink MD, Boston, MA)	8	8	5	2
115 (Kevin Gleeson MD, Hershey, PA)	2	2	2	1
117 (Marilyn Haupt MD, Detroit, MI)	3	3	1	0
118 (Amy Imm MD, Columbus, OH)	2	2	1	0
119 (Stephen Jenkinson MD, San Antonio, TX)	6	6	4	2
120 (Tim Kotschwar Pharm. D., Springfield, MO)	16	15	11	3
121 (Nazir Memon MD, Absecon, NJ)	3	3	3	1

122 (Burt Meyers MD, New York, NY)	3	2	0	0
123 (Michael Niederman MD, Mineola, NY)	6	6	5	0
124 (Michael Nelson MD, Kansas City, MO)	11	11	11	7
125 (Jose Plouffe MD, Columbus, OH)	24	23	15	5
126 (Jay Redington MD, Denver, CO)	2	2	2	0
127 (Harry Gallis MD, Durham, NC)	4	4	3	1
128 (Michael Scheld MD, Charlottesville, VA)	3	3	3	1
129 (Robert Siegal MD, Bronx, NY)	1	1	1	1
131 (Dennis Mikolich MD, Cranston, RI)	3	3	2	1
132 (Charles van Hook MD, Longmont, CO)	6	6	4	3
133 (Randall Willis MD, Harrogate, TN)	8	8	7	1
134 (Sandra Willsie MD, Kansas City, MO)	6	6	5	2
135 (Marcus Zervos MD, Royal Oak, MI)	7	7	6	1
110 (Joseph Palladino Pharm. D., Williamsville, NY)	6	6	4	0
106 (Judith Hyatt Pharm. D., Buffalo, NY)	4	4	3	2
337 (Stephen Storfer MD, St. Louis, MO)	8	8	8	1
340 (Mark Doner MD, High Point, NC)	5	5	3	2
338 (Henry Fraimow MD,	2	2	1	0

Philadelphia, PA)				
339 (Rick Player MD, Birmingham, AL)	6	6	5	3
348 (Gregory Peterson DO, Des Moines, IA)	5	5	4	1
Total	206	202	150	53

Number of Patients in Comparator Group

Center Number	Randomized	Received Treatment	Clinically Evaluable	Bacteriologically Evaluable
116	19	19	18	11
107	4	4	2	0
108	1	1	0	0
109	1	1	0	0
237	4	4	4	1
111	4	4	3	0
112	4	4	0	0
113	10	10	6	0
114	7	5	4	1
115	3	3	3	0
117	3	3	3	0
118	2	2	2	0
119	6	5	4	2
120	16	14	6	4
121	4	4	3	0
122	2	2	0	0
123	6	6	2	0
124	12	12	10	4
125	26	25	15	5
126	2	2	1	0
127	2	2	1	1
128	2	2	1	0
129	1	1	1	1
130	1	1	0	0
131	3	3	3	3
132	4	4	4	1

133	8	8	7	2
134	5	5	4	1
135	7	7	5	2
110	7	7	6	1
106	5	5	4	1
337	8	8	6	2
340	6	6	5	0
338	1	1	1	1
339	6	6	4	0
348	5	5	3	0
Total	207	201	141	44

Demographic Data for Sponsor Clinically Evaluable Patients

	Azithromycin			Comparator		
	Male	Female	Total	Male	Female	Total
# of Patients	88	62	150	88	53	141
Age Group (years)						
16-44	17	19	36	20	11	31
45-64	27	15	42	24	21	45
>=65	44	28	72	44	21	65
Race						
White	68	45	113	66	41	107
Black	17	15	32	19	12	31
Asian	0	1	1	0	0	0
Other	3	1	4	3	0	3

Number of Dosing Days for IV Therapy--Sponsor Clinically Evaluable Patients

		Comparator		
Days of IV Dosing	Azithromycin	Cefuroxime	Cefuroxime + Erythromycin	Combined
1	0	0	0	0
2	26 (17)	9 (12)	6 (9)	15 (11)
3	49 (33)	25 (34)	29 (43)	54 (38)
4	40 (27)	14 (19)	13 (19)	27 (19)
5	28 (19)	14 (19)	6(9)	20 (14)
6	4 (3)	3 (4)	10 (15)	13 (9)
7	2 (1)	5 (7)	2 (3)	7 (5)
8	1 (1)	3 (4)	1 (1.5)	4 (3)
9	0	0	0	0
10	0	0	1 (1.5)	1 (1)
Total treated	150	73	68	141
Mean Duration	3.63	4.05	4.01	4.04

MO Note: Although the proposed package insert states patients should receive at least 2 days of i.v. therapy, the majority (95%) of the patients in this study received between 2 and 5 days of i.v. therapy.

Number of Dosing Days for IV and Oral Therapy---Sponsor Clinically Evaluable Patients

Days of Dosing	Azithromycin n (%)	Cefuroxime n (%)	Cefuroxime +Erythromycin n (%)	Combined Comparator n (%)
1	0	0	0	0
2	0	2 (3)	0	2 (1.4)
3	4 (3)	1 (1.4)	0	1 (1)
4	8 (5)	1 (1.4)	2 (3)	3 (2)
5	5 (3)	0	3 (4.4)	3 (2)
6	6 (4)	1 (1.4)	1 (1.5)	2 (1.4)
7	17 (11)	3 (4)	2 (3)	5 (3.5)
8	12 (8)	5 (7)	2 (3)	7 (5)
9	18 (12)	21 (29)	9 (13)	30 (21)
10	78 (52)	32 (44)	23 (34)	55 (39)
11-15	2 (1)	7 (10)	23 (34)	30 (21)
16 or more	0	0	3 (4.4)	3 (2.1)
Total treated	150	73	68	141
Mean Duration	8.57	9.16	10.29	9.71

Reason for exclusion from sponsor evaluable patients

	Number of patients randomized (% of randomized)	
	Azithromycin	Comparator
Randomized patients	206	207
Reason for exclusion from ITT		
Did not receive study drug	4 (1.9)	6 (2.9)
Inappropriate diagnosis	7 (3.4)	3 (1.5)
Concomitant antibiotics	6 (2.9)	3 (1.5)
Failure with insufficient dosing	7 (3.4)	1 (0.5)
Noncompliance	5 (2.4)	16 (7.7)
Resistant Baseline Pathogen	2 (1.0)	2 (1.0)
Prior antibiotic therapy	1 (1.0)	2 (1.0)
Visits outside of windows*	2 (1.0)	5 (2.4)
Lost to follow-up	6 (2.9)	7 (3.4)
Other early withdrawals	16 (7.8)	21 (10.1)
Total excluded from ITT	56 (27.2)	66 (31.9)
Total Clinically Evaluable for either visit	150 (82.8)	141 (68.1)
4-6 Week Evaluable Patients	130 (63.1)	122 (58.9)
(20 patients in the azithromycin arm and 19 in the comparator arm did not follow-up at the appropriate times).		
10-14 Day Evaluable Patients	137 (66.5)	131 (63.2)
(13 patients in the azithromycin arm and 10 patients in the comparator arm did not follow-up at the appropriate times.)		
Evaluable for Bacteriological Outcome	53 (25.73)	44 (21.26)

*A window of 9-18 days post-therapy was used for the 10-14 day post-therapy follow-up visit.

A window of 25-50 days post-therapy was used for the 4-6 weeks post-therapy follow-up visit.

MO note: These patients were considered evaluable by the MO depending on the clinical reason for the visit. For example if early visits were due to worsening symptoms the patient would be considered an evaluable failure. Therefore, patients with "visits outside of the appropriate window" were reviewed to find out the reason for the timing of the visit.

CLINICAL OUTCOME--SPONSOR EVALUABLE PATIENTS

	Number of Patients (% of total) 10-14 Days Post-Therapy	
Clinical outcome	Azithromycin	Comparator*
Cure	61 (44.5)	55 (42.0)
Improvement	45 (32.9)	42 (32.1)
Cure + Improvement	106 (77.4)	97 (74.0)
Failure	31 (22.6)	34 (26.0)
Total included	137	131

*Comparative treatment consisted of IV cefuroxime followed by oral cefuroxime with optional addition of IV or oral erythromycin.

Clinical Outcomes at 10-14 Days Post-Therapy by Baseline Pathogen--Sponsor Evaluable Patients, Azithromycin Arm

		Number of Patients(% of Pathogen Total)			
Pathogen	Total	Cure	Improvement	Cure + Improvement	Failure
Streptococcus pneumoniae	30	17 (56.7)	9 (30)	26(80.7)	4(13.3)
Haemophilus influenzae	15	7 (46.7)	5 (33.3)	12(80)	3(20)
Staphylococcus aureus	5	2 (40)	2 (40)	4(80)	1(20)
Moraxella catarrhalis	3	1	1	2	1
Mycoplasma pneumoniae	3	2	0	2	1
Bordetella bronchiseptica	1	0	1	1	0
Escherichia coli	0	0	0	0	0
Klebsiella oxytoca	0	0	0	0	0
Legionella pneumophila	1	0	0	0	1
Enterobacter aerogenes	0	0	0	0	0

Note: Patients with more than one pathogen at baseline are listed once for each pathogen identified.

The patients infected with an atypical pathogen are those with clinical evidence of infection only.

Clinical Outcomes at 10-14 Days Post-Therapy by Baseline Pathogen--Sponsor Evaluable Patients, Comparator Arm

	Number of Patients(% of Pathogen Total)				
Pathogen	Total	Cure	Improvement	Cure + Improvement	Failure
Streptococcus pneumoniae	27	12 (44.4)	8 (29.6)	20(74.1)	7(25.9)
Haemophilus influenzae	10	2	6	8	2
Staphylococcus aureus	3	1	0	1	2
Moraxella catarrhalis	3	0	1	1	2
Mycoplasma pneumoniae	2	1	0	1	1
Bordetella bronchiseptica	0	0	0	0	0
Escherichia coli	2	1	0	1	1
Klebsiella oxytoca	1	1	0	1	0
Legionella pneumophila	0	0	0	0	0
Enterobacter aerogenes	1	0	0	0	1

Note: Patients with more than one pathogen at baseline are listed once for each pathogen identified.

The patients infected with an atypical pathogen listed above are only those with positive cultures.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients With Evidence of Infection with *Mycoplasma pneumoniae*--Sponsor Evaluable Patients, Azithromycin Arm.

	Number of Patients(% of Category Total)				
Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
Culture Only	2	1	0	1	1
Culture + IgM	1	1	0	1	0
Culture + IgG	0	0	0	0	0
IgM Only	5	3	1	4	1
IgG Only	1	0	1	1	0
Total Patients	9	5	2	7	2

Note: Culture = isolation of organism with PCR confirmation of M. pneumoniae.

IgM titer>=10, IgG titer>=4-fold rise in titer from baseline.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients With Evidence of Infection with *Mycoplasma pneumoniae* -Sponsor Evaluable Patients, Comparator Arm.

		Number of Patients(% of Category Total)			
Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
Culture Only	0	0	0	0	0
Culture + IgM	1	0	0	0	1
Culture + IgG	1	1	0	1	0
IgM Only	1	0	1	1	0
IgG Only	2	1	1	2	0
Total Patients	5	2	2	4	1

Note: Culture = isolation of organism with PCR confirmation of M. pneumoniae. IgM titer>=10, IgG titer>=4-fold rise in titer from baseline.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients with Evidence of Infection with *Chlamydia pneumoniae*--Sponsor Evaluable Patients, Azithromycin Arm.

		Number of Patients(% of Category Totals)			
Evidence of infection	Total	Cure	Improvement	Cure + Improvement	Failure
IgG Only	11	4 (36.4)	4 (36.4)	8 (73.7)	3 (27.3)
IgG + IgM	1	1	0	1	0
Total Patients	12	5 (41.7)	4 (33.3)	9 (75.0)	3 (25.0)

Note: IgM>=20, IgG>512, or >=4-fold rise in titer from baseline.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients with Evidence of Infection with *Chlamydia pneumoniae*--Sponsor Evaluable Patients, Comparator Arm.

		Number of Patients(% of Category Totals)			
Evidence of infection	Total	Cure	Improvement	Cure + Improvement	Failure
IgG Only	18	9 (50.0)	5 (27.8)	14(77.8)	4(22.2)
IgG + IgM	0	0	0	0	0
Total patients	18	9 (50.0)	5 (27.8)	14(77.8)	4(22.2)

Clinical Outcomes at 10-14 days Post-Therapy for Patients with Evidence of Infection with Legionella--Sponsor Clinically Evaluable Patients, Azithromycin Arm.

	Number of Patients(% of Category Total)				
Evidence of infection	Total	Cure	Improvement	Cure + Improvement	Failure
Culture + IgG	1	0	0	0	1
IgG only	3	1	2	3	0
Total Patients	4	1	2	3	1

Clinical Outcomes at 10-14 days Post-Therapy for Patients with Evidence of Infection with Legionella--Sponsor Clinically Evaluable Patients, Comparator Arm.

	Number of Patients(% of Category Total)				
Evidence of infection	Total	Cure	Improvement	Cure + Improvement	Failure
Culture + IgG	0	0	0	0	0
IgG only	5	0	4	4	1
Total Patients	5	0	4	4	1

MO Note on Atypical Pathogen Patients: Serology was the primary objective criteria used for defining infection with an atypical pathogen. The medical officer asked the sponsor to separate the data on these patients from the rest of the application so that an in-depth review could be performed. Patients were reviewed to assess clinical, radiographic and laboratory parameters. All patients had radiographic evidence of pneumonia. No inconsistencies among patients with atypical pathogens were identified. In general, the investigator assessment of the entry x-ray matched that of the radiologist.

MO Note: The 4-6 week post-therapy responses are similar to the 10-14 day post-therapy outcomes. A review of the patient failures in study 618 shows that the majority of failures occurred before the long-term follow-up. Two patients in the azithromycin arm failed at the long-term follow-up, and 2 patients in the comparator (cefuroxime) arm failed at the long-term follow-up. This suggests that the patients in the azithromycin arm did not have a disproportionately favorable outcome at the long-term follow-up which might have occurred if infection was merely suppressed at the short-term follow-up. If this were the case, more failures in the comparator arm would also be expected at the short-term follow-up. Given the long tissue half-life of azithromycin, 68 hours, this was a concern. However, the data support the use of the 10-14 day post-therapy follow-up as the test of cure.

Bacteriological outcomes (1) by baseline pathogens among the bacteriologically evaluable patients at the final visit (4-6 weeks post-therapy) --Sponsor Evaluable Patients in Study 0618, Azithromycin Arm

	Number of Patients(% of Pathogen Total)		
Pathogen	Total	Eradication	Persistence
Streptococcus pneumoniae	31	30 (96.8)	1 (3.2)
Haemophilus influenzae	16	15 (93.8)	1 (6.2)
Staphylococcus aureus	5	4	1
Moraxella catarrhalis	3	3	0
Mycoplasma pneumoniae	3	2	1
Bordetella bronchiseptica	1	1	0
Escherichia coli	0	0	0
Klebsiella oxytoca	0	0	0
Legionella pneumophila	1	1	0
Enterobacter aerogenes	0	0	0

(1) 60 Pathogens isolated from 53 bacteriologically evaluable patients.

Bacteriological outcomes (1) by baseline pathogens among the bacteriologically evaluable patients at the final visit (4-6 weeks post-therapy) --Sponsor Evaluable Patients, ComparatorArm

	Number of Patients(% of Pathogen Total)		
Pathogen	Total	Eradication	Persistence
Streptococcus pneumoniae	28	26 (92.9)	2. (7.1)
Haemophilus influenzae	11	8 (72.7)	3 (27.3)
Staphylococcus aureus	4	2	2
Moraxella catarrhalis	3	2	1
Mycoplasma pneumoniae	2	1	1
Bordetella bronchiseptica	0	0	0
Escherichia coli	2	2	0
Klebsiella oxytoca	1	1	0
Legionella pneumophila	0	0	0
Enterobacter aerogenes	1	1	0

(1) 52 Pathogens isolated from 44 bacteriologically evaluable patients.

Medical Officer's Efficacy Results

Evaluable patients were reviewed for appropriateness of inclusion. No changes were made in this population from the sponsor's analysis. Non-evaluable patients were reviewed and changes were made. A list of patients originally classified as non-evaluable by the sponsor and changed to evaluable by the medical officer follows. The reasons for the initial classification by the sponsor and the reasons for the MO changes are listed.

MO Evaluability Changes for Study 618

Center #	Patient #	Change
125		Eval Cure
106		Eval Cure
120		Eval Cure
120		Eval Cure
120		Eval Cure
135		Eval Fail
340		Eval Fail
348		Eval Cure
135		Eval Cure

Total Changes: 9 patients were changed from non-evaluable to evaluable. Of these, 2 were failures, 7 were cures. Among the cures, 5 were from the comparator arm, 2 from the azithromycin arm. Both failures were in the comparator arm. The sponsor carried forward failures in all analyses. Even if patients' follow-up visits were outside of the specified windows, if the investigator considered the patient a failure, this was taken by the sponsor as well. This explains why there are few MO changes to the evaluable population. The MO considers the sponsor data valid as a result of this observation.

Explanation of changes

Center 125, Patient [redacted] The patient received two days of study drug in the hospital and was discharged on oral study medication. Follow-up showed resolution of signs and symptoms of pneumonia. The medical officer considered this an evaluable cure. It is unclear why the sponsor considered this patient non-evaluable. Study drug = azithromycin.

Center 106, Patient [redacted] This patient completed the study protocol without incident and with complete resolution of signs and symptoms of pneumonia. The medical officer considered this patient an evaluable cure. It is unclear why the sponsor deemed this patient non-evaluable. Study drug = azithromycin.

Center 120, Patient [redacted] This patient showed improvement in signs and symptoms of pneumonia. The medical officer considered this an evaluable cure. Study drug = comparator.

Center 120, Patient [redacted] This patient showed complete resolution of pneumonia during follow-up. The medical officer considered this an evaluable cure. Study drug = comparator.

Center 120, Patient [redacted] The sponsor recorded this patient as non-evaluable because of failure to make the final scheduled visit due to an out-of-town trip. All signs and symptoms of pneumonia resolved, however. The medical officer considered this an evaluable cure. Study drug = comparator.

Center 135, Patient [redacted] This patient was considered non-evaluable by the sponsor because of "inadequate response to study med." The patient required a change in therapy after two days of study; therefore, the medical officer considered this an evaluable treatment failure. Study drug = comparator.

Center 340, Patient [redacted] The patient was on study drug for 5 days and was considered nonevaluable by the sponsor for "failure to improve on therapy." The medical officer considered this an evaluable failure. Study drug = comparator.

Center 348, Patient [redacted] The patient's signs and symptoms resolved by the first post-therapy follow-up. The sponsor recorded this patient as non-evaluable because of failure to show up at the long-term follow-up visit. The medical officer considered this an evaluable cure. Study drug = comparator.

Center 135, Patient [redacted] The medical officer considered this patient an evaluable cure at the 10-14 day post-therapy follow-up because all signs and symptoms resolved. She was considered non-evaluable by the sponsor at the long-term follow-up because she died of an unrelated event. Study drug = comparator.

CLINICAL OUTCOME--MO EVALUABLE PATIENTS--ALL PATIENTS
10-14 Days Post-Therapy Visit

	Number of Patients (% of total)	
Clinical Outcome	Azithromycin	Comparator*
Cure	64 (46.0)	61 (44.2)
Improvement	44 (31.7)	41 (29.7)
Cure + Improvement	108 (77.7)	102 (73.9)
Failure	31 (22.3)	36 (26.1)
Total Evaluable	139	138
95% Confidence Interval of difference in Cure + Improvement	(-7%, 14.6%)	

*Comparative treatment consisted of IV cefuroxime followed by oral cefuroxime with optional addition of IV or oral erythromycin.

MO Note: Among the MO changes there were two patients with atypical pneumonia that were changed to cures. Both patients had evidence of Chlamydia pneumoniae infection. One patient had been randomized to the azithromycin arm, the other to the comparator arm. No significant change in the sponsor outcome is observed if the MO changes are made to the sponsor data; therefore, tables showing MO results for the subgroup of patients with atypical pneumonia will not be presented.

MO Note on bacteremic patients: A total of 28 patients in study 0618 had positive blood cultures. All were positive for Streptococcus pneumoniae. In the azithromycin arm, 6/15 (40%) were considered cured, 5/15 (33%) were considered improved yielding an overall favorable rate of 11/15 (73%) while 4/15 (27%) failed. In the comparator arm, 6/13 (46%) were considered cured, 4/13 (31%) were considered improved yielding an overall favorable rate of 10/13 (77%) while 3/13 (23%) failed.

Subgroup Analysis of Efficacy in Medical Officer's Evaluable Patients

Subgroup	n cured / N evaluable	% cured	n cured / N evaluable	% cured	p-value Fisher's Exact	p-value CMH
	azithromycin		comparator			
Female	49 / 61	80%	37 / 52	71%	0.276	0.466
Male	59 / 78	76%	65 / 86	76%	1.000	
< 45	30/ 32	94%	24 / 30	80%	0.141	0.459
45-65	32 / 39	82%	31 / 44	70%	0.305	
>65	46 / 68	68%	47 / 64	73%	0.568	
white	78 / 105	74%	74 / 107	69%	0.448	0.453
black	28 / 29	97%	25 / 28	89%	0.352	
other	2 / 5	40%	3 / 3	100%	0.196	
Days on IV						
1 day	0 / 0		0 / 1	0%		0.769
2 days	21 / 25	84%	12 / 15	80%	1.000	
3 days	35 / 45	78%	44 / 50	88%	0.272	
4 days	25 / 37	68%	16 / 27	59%	0.600	
5 days	22 / 26	85%	15 / 19	79%	0.704	
6 days	4 / 4	100%	8 / 13	62%	0.261	
7-14 days	1 / 2	50%	7 / 13	54%	1.000	

Stat Note: No statistically significant differences were found when comparing subgroups of gender, age, race, or days on IV.

MO Note: An MO bacteriological outcomes table will not be shown here since the only changes in clinical outcome were to reclassify two non-evaluable azithromycin-treated patients as evaluable successes. Refer to the bacteriological outcomes table included in the sponsor's results presented above.

Safety

Summary of Adverse Events for study 0618 (1) by body system -- All treated patients

	Number of Patients (2) with an adverse event (% of safety evaluable)				
	Azithromycin	Cefuroxime Only	Cefuroxime Plus Erythromycin	Comparator (3)	P-Value Azi vs Comp (5)
Number of Patients					
Evaluable for safety	202 (100.0%)	105 (100.0%)	96 (100.0%)	201 (100.0%)	
With adverse event	165 (81.7%)	84 (80.0%)	90 (93.8%)	174 (86.6%)	
Discontinued due to adverse event (4)	29 (14.4%)	8 (7.6%)	19 (19.8%)	27 (13.4%)	
Adverse Events by Body Systems					
body as a whole	93 (46.0%)	43 (41.0%)	59 (61.5%)	102 (50.7%)	0.37
cardiovascular	27 (13.4%)	14 (13.3%)	13 (13.5%)	27 (13.4%)	1.00
digestive	71 (35.1%)	39 (37.1%)	60 (62.5%)	99 (49.3%)	0.005
endocrine	0 (0%)	1 (1.0%)	0 (0%)	1 (0.5%)	0.50
hemic and lymphatic	10 (5.0%)	4 (3.8%)	6 (6.3%)	10 (5.0%)	1.00
metabolic and nutritional	19 (9.4%)	11 (10.5%)	16 (16.7%)	27 (13.4%)	0.21
skin and appendages	17(8.4%)	5 (4.8%)	13(13.5%)	18 (9.0%)	0.86
musculoskelatal	11 (5.4%)	7 (6.7%)	5 (5.2%)	12 (6.0%)	0.83
nervous	56 (27.7%)	24 (22.9%)	33 (34.4 %)	57 (28.4%)	0.91
respiratory	67 (33.2%)	32 (30.5%)	35 (36.5%)	67 (33.3%)	1.00
special senses	9 (4.5%)	2 (1.9%)	5 (5.2%)	7 (3.5%)	0.80
urogenital	10 (5.0%)	8 (7.6%)	6 (6.3%)	14 (7.0%)	0.41

(1) Adverse events which occurred within 35 days post-therapy or at any time while patient was on study (whichever was the latest observation).
(2) Patients counted once within each body system for multiple adverse events within the same body system.
(3) Comparative treatment consisted of IV cefuroxime followed by oral cefuroxime with optional addition of IV or oral erythromycin.
(4) Number of patients who discontinued due to adverse events or laboratory abnormality.
(5) P-Value based upon Fisher's exact test

Stat Note: The azithromycin treated group experienced a statistically lower percent in the number of patients experiencing adverse events in the digestive system when compared with the comparator arm (p-value = 0.005). As can be seen in the table above, azithromycin is comparable to cefuroxime alone with 35.1% versus 37.1% reporting adverse events in the digestive system in the respective treatment arms. In contrast, 62.5% of the patients in the cefuroxime plus erythromycin arm experienced adverse events in the digestive system.

Table: Incidence of adverse events greater than or equal to 1% for all treated patients for protocol 0618 in descending sequence by percent of the azithromycin-treated patients

System	Adverse Experiences	Azithromycin IV N = 202	Azithromycin IV%	Comparator N = 201	Comparator %
Body	headache	35	17.3%	30	14.9%
Digestive	constipation	29	14.4%	30	14.9%
Nervous	insomnia	27	13.4%	39	19.4%
Digestive	diarrhea	20	9.9%	28	13.9%
Digestive	nausea	20	9.9%	32	15.9%
Body	injection site reaction - infect/inflam	18	8.9%	27	13.4%
Respiratory	respiratory disorder	18	8.9%	12	6.0%
Body	injection site reaction - pain	16	7.9%	16	8.0%
Nervous	anxiety	15	7.4%	11	5.5%
Respiratory	pneumonia	14	6.9%	12	6.0%
Digestive	vomiting	13	6.4%	18	9.0%
Body	chest pain	12	5.9%	19	9.5%
Digestive	dyspepsia	12	5.9%	13	6.5%
Body	injection site reaction - device complication	11	5.4%	9	4.5%
Body	pain	11	5.4%	11	5.5%
Body	abdominal pain	10	5.0%	11	5.5%
Body	back pain	10	5.0%	12	6.0%
Respiratory	dyspnea	10	5.0%	12	6.0%
Respiratory	pleural effusion	9	4.5%	12	6.0%
Body	fever	8	4.0%	3	1.5%
Cardiovascular	hypertension	8	4.0%	7	3.5%
Musculoskeletal	arthralgia	8	4.0%	7	3.5%
Respiratory	rhinitis	8	4.0%	6	3.0%
Nervous	agitation	6	3.0%	7	3.5%
Nervous	dizziness	6	3.0%	4	2.0%
Respiratory	epistaxis	6	3.0%	3	1.5%
Skin and skin structures	rash	6	3.0%	6	3.0%
Metabolic and nutritional	edema	5	2.5%	4	2.0%
Metabolic and nutritional	hypokalemia	5	2.5%	5	2.5%
Respiratory	asthma	5	2.5%	1	0.5%
Respiratory	pharyngitis	5	2.5%	6	3.0%
Cardiovascular	congestive heart failure	4	2.0%	8	4.0%
Hemic and Lymphatic	anemia	4	2.0%	4	2.0%
Nervous	confusion	4	2.0%	3	1.5%
Respiratory	bronchitis	4	2.0%	5	2.5%
Skin and skin structures	skin ulcer	4	2.0%	2	1.0%
Cardiovascular	arrhythmia	3	1.5%	2	1.0%
Digestive	gastritis	3	1.5%	2	1.0%
Respiratory	cough increased	3	1.5%	4	2.0%
Respiratory	pleural disorder	3	1.5%	6	3.0%
Respiratory	sinusitis	3	1.5%	6	3.0%
Skin and skin structures	skin disorder	3	1.5%	4	2.0%
Special senses	taste perversion	3	1.5%	0	0.0%
Cardiovascular	myocardial infarction	2	1.0%	0	0.0%
Digestive	flatulence	2	1.0%	5	2.5%
Metabolic and nutritional	dehydration	2	1.0%	2	1.0%
Metabolic and nutritional	hypophosphatemia	2	1.0%	1	0.5%
Metabolic and nutritional	perpheral edema	2	1.0%	8	4.0%
Metabolic and nutritional	weight gained	2	1.0%	0	0.0%
Musculoskeletal	bone disorder	2	1.0%	2	1.0%
Nervous	somnolence	2	1.0%	3	1.5%
Respiratory	hemoptysis	2	1.0%	2	1.0%
Respiratory	hypoventilation	2	1.0%	1	0.5%
Respiratory	hypoxia	2	1.0%	2	1.0%
Skin and skin structures	herpes simplex	2	1.0%	4	2.0%
Special senses	abnormal vision	2	1.0%	3	1.5%
Special senses	ear pain	2	1.0%	1	0.5%
Urogenital	kidney function abnormal	2	1.0%	2	1.0%

Protocol 93CE33-0625:

AZITHROMYCIN IN THE TREATMENT OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA. A MULTICENTER OPEN TRIAL.

Study Dates: 23 MAR 94 to 4 JULY 95

Study Objective: The objective of this study was to evaluate the safety and efficacy of intravenous azithromycin against susceptible pathogens in the treatment of hospitalized patients with community-acquired pneumonia (CAP).

Methods

Study Design: This study was conducted as a multicenter, open-label, noncomparative trial of azithromycin. Patients were to be evaluated at baseline, daily during hospitalization, on Day 3 of therapy, every 5 to 7 days during therapy, 10 to 14 days post-therapy, and 4 to 6 weeks post-therapy.

Inclusion Criteria:

- Age at least 16 years
- Women of childbearing potential should have had a negative urine pregnancy test
- Patients must have required hospitalization
- Clinically and radiographically/microbiologically documented CAP
- Informed written consent

Exclusion Criteria:

- Pregnant or lactating women
- Known hypersensitivity or intolerance to beta-lactam or macrolide antibiotics
- Patients with active peptic ulcers, gastrectomy, or other conditions affecting drug absorption
- Evidence or history of significant hematological, renal, cardiovascular, or hepatic disease, AIDS, HIV infection, or metastatic tumor. This includes the following concomitant medical conditions:
    a. Leukopenia (absolute neutrophil count < 1,000/cu.mm); thrombocytopenia (platelet count < 75,000/cu.mm); anemia (Hgb < 9g/dL); or known bleeding disorder.
    b. Creatinine clearance , 25 mL/min
    c. Alkaline phosphatase > 2 times the laboratory range upper limit of normal; AST(SGOT) or ALT(SGPT) > 2 times the laboratory upper limit of normal; or, total bilirubin > 1.5 mg/dL.
- Patients receiving chemo or immunosuppressive therapy.
- Known drug or alcohol dependence.

- Presence of infection that may have required treatment with an antibiotic other than the study drugs.
- Treatment with any other potentially effective antibiotic within 24 hours prior to enrollment.
- Treatment with another investigational drug within four (4) weeks prior to enrollment, or previous enrollment in this protocol.
- Chronic bronchitis, bronchiectasis, or chronic obstructive pulmonary disease (COPD) in the absence of an acute pneumonia.
- Evidence of any of the following:

  a. Predominance of Gram negative rod other than *Haemophilu* on sputum Gram's stain. Slides must have been read prior to randomization of the patient.

  b. Signs and symptoms suggestive of infection with a Gram negative organism other than *Haemophilus.*

  c. Aspiration pneumonia

  d. Postobstructive pneumonia
- Suspected septic shock characterized by fever and systolic blood pressure < 90 mm Hg or mean arterial pressure < 70 mm Hg.
- Rapidly progressive underlying disease that precludes evaluation of therapy.
- Presence of coma or requirement for endotracheal intubation.
- Use within the past 14 days prior to study enrollment, or concomittant use of terfenadine or loratidine. Also use within the past 30 days prior to study enrollment, or concomittant use of astemizole.
- Cystic fibrosis
- Hospitalization within the preceding 14 days.

MO Comment: These criteria are consistent with the 1992 Guidelines for the Evaluation of Anti-infective Drug Products.

The Clinical and bacteriological evaluations are the same as those described for the preceding protocol. Methods for culture and serology were also the same as previously described.

Study Drug Administration

Azithromycin was to be administered as 500 mg IV in 250mL 0.45% or 0.9% saline over 1 hour QD or 500mL 0.9% saline over 3 hours QD for 2 to 5 days (minimum of two doses), depending upon the patient's clinical response, followed by azithromycin, 500 mg PO QD, to complete a total of 7 to 10 days of therapy.

Sponsor's Efficacy Results

Enrollment by Center

Center (Investigator, City)	Randomized	Received Treatment	Evaluable	Bacteriologically Evaluable
206 (Paul Arnow MD, Chicago, IL)	18	17	8	7
209 (Leigh Ann Callahan MD, Augusta, GA)	1	1	0	0
213 (John Gezon MD, Salt Lake City, UT)	25	25	15	13
216 (Robert J. Lapidus MD, Wheat Ridge, CO)	1	1	0	0
217 (David M. Letzer DO, Milwaukee, WI)	1	1	0	0
218 (Darwin L. Palmer MD, Albuquerque, NM)	22	22	11	6
219 Alex Pareigis MD, Moline, IL)	9	9	4	3
222 (Douglas Schwartz MD, Cleveland, OH)	16	16	7	5
223 Bruce Sherman MD, Cleveland, OH)	27	27	9	5
221 (Richard Root MD, Seattle, WA)	1	1	0	0
224 (David Wagner MD, Milwaukee, WI)	4	4	1	1
236 (Karl Beutner MD, Vallejo, CA)	3	3	2	0
215 (Monroe Karetzky MD, Newark, NJ)	7	7	3	1
211 (Carlos Dela Garza MD, Hickory, NC)	3	3	0	0

214 (Kirk Jacobson MD, Eugene, OR)	7	7	4	3
220 (Julio Ramirez MD, Louisville, KY)	9	9	4	2
229 (Byungse Suh MD, Philadelphia, PA)	11	11	6	4
226 William Alto MD, Grand Junction, CO)	4	4	2	1
230 (Andrew Villanueva MD, Burlington, MA)	2	2	0	0
233 (Brooke Nicotra MD, Tyler, TX)	3	3	3	3
228 (David Smith MD, Kansas City, MO)	3	3	1	1
231 (Rodney Wishnow MD, Long Beach, CA)	12	12	10	10
227 (Larry Danzinger Pharm. D., Chicago, IL)	2	2	0	0
235 (Robert Salata MD, Cleveland, OH)	1	1	0	0
208 (Keith Ironside MD, Portland, OR)	1	1	0	0
207 (Kerry Cleveland MD, Memphis, TN)	5	5	0	0
234 (Warren Whitlock MD, Fort Gordon, PA)	11	11	3	0
349 (Charles Oster MD, Washington, DC)	1	1	0	0
350 (Kalpaletha Guntupali MD, Houston, TX)	1	1	1	1
351 (William Holloway MD, Wilmington, DE)	2	2	0	0

Total # enrolled: 213
Received Study Medication: 212
Included in ITT Analysis:
10-14 Day Visit: 176
4-6 Week Visit: 168
Included in Evaluable Cases Analysis:
10-14 Day Visit: 84
(92 patients were considered nonevaluable at the 10-14 day visit for the following reasons: No baseline pathogen--61; Visits outside of window--23; Concomitant or prior antibacterial therapy--4; Noncompliance--3; Incorrect dosage received--1.)
4-6 Week Visit: 85
Total Clinically Evaluable: 94
Evaluable for Bacteriological Outcome: 66
Assessed for Safety: 212

Demographic Data Sponsor Evaluable Patients:

	Azithromycin		
	Male	Female	Total
Number of Patients	63	31	94
Age (Years)			
Range			
Mean	57.63	57.81	57.69
Race			
White	40	17	57
Black	14	12	26
Other	9	2	11

Baseline pathogens among the 94 patients that were considered evaluable by the sponsor at either the 10-14 day post-therapy visit or the 4-6 week post-therapy visit.

Pathogen (2)	Number of Patients (1)
	Azithromycin
# Evaluable Patients	94
Streptococcus pneumoniae	38 (40.4%)
Haemophilus influenzae	27 (28.7%)
Moraxella catarrhalis	7 (7.5%)
Staphylococcus aureus	5 (5.3%)
Mycoplasma pneumoniae	2 (2.1%)
Klebsiella pneumoniae	2 (2.1%)
Escherichia coli	1 (1.1%)
Enterobacter cloacae	1 (1.1%)
Patients with a Single Pathogen	51
Patients with Multiple Pahogens	15

1) Patients with more than one pathogen at baseline are listed once for each pathogen identified.
2) Culture negative patients with other evidence of infection with an atypical pathogen are not included.

Number of Dosing Days for IV Therapy

	Number of Patients:	
Days of IV Dosing	All treated patients	Evaluable patients
1	12(5.7%)	0
2	46(21.7%)	23(24.5%)
3	78(36.8%)	32(34.0%)
4	33(15.6%)	17(18.1%)
5	37(17.5%)	19(20.2%)
6	6(2.8%)	3(3.2%)
Total	212	94
Mean Duration of therapy:	3.26	3.44

Number of Dosing Days for IV and Oral Therapy

	Number of Patients:	
Days of Dosing	All treated patients	Evaluable patients
1	12(5.7%)	0
2	7(3.3%)	0
3	5(2.4%)	3(3.2%)
4	9(4.2%)	1(1.1%)
5	4(1.9%)	1(1.1%)
6	6(2.8%)	2(2.1%)
7	27(12.7%)	9(9.6%)
8	21(9.9%)	13(13.8%)
9	19(9.0%)	7(7.4%)
10	82(38.7%)	50(53.2%)
11-15	19(9.0%)	8(8.5%)
16 or more	1(0.5%)	0
Total	212	94
Mean Duration of Therapy	8.13	9.10

A total of 119 patients were excluded from the evaluable cases analysis. The reasons for exclusion and the number of patients are listed below.

Reason	# excluded
Did not receive study drug	1(0.5%)
Inappropriate primary diagnosis	5(2.4%)
Concomitant antibacterial therapy	3(1.4%)
Failure with insufficient dosing	1(0.5%)
Noncompliance to study dosing	3(1.4%)
No evidence of baseline pathogen	68(31.9%)
Prior antibiotic therapy	3(1.4%)
Visits outside of window*	7(3.3%)
Lost to follow up	9(4.2%)
Early Withdrawal	19(8.9%)
Total excluded:	119
Total evaluable at either follow-up visit	94
Evaluable at 10-14 days post-therapy	84
Evaluable at 4-6 weeks post-therapy	85

*A window of 9-18 days post-therapy was used for the 10-14 day post-therapy follow-up visit. A window of 25-50 days post-therapy was used for the 4-6 week post therapy follow-up visit.

MO note: These patients will be considered evaluable by the MO depending on the clinical reason for the visit. For example if early visits were due to worsening symptoms the patient would be considered an evaluable failure.

CLINICAL OUTCOMES--SPONSOR EVALUABLE PATIENTS

Clinical Outcome	10-14 Day Post-Therapy	4-6 Week Post-Therapy
Cure	50 (59.5)	73 (85.9)
Improved	24 (28.6)	N/A
Cure + Improved	74 (88.1)	N/A
Failure	10(11.9)	12 (14.1)

10-14 Day Post-Therapy Outcome by Duration of IV Dosing--Sponsor Evaluable Patients

Days IV Dosing	Cured	Improved	Cure + Improvement	Failure	Total
2	14 (70)	6 (30)	20(100%)	0	20
3	15 (50)	10 (33.3)	25(83.3%)	5(16.7%)	30
4	8 (61.5)	4 (30.8)	12(92.3%)	1(7.7%)	13
5	13 (68.4)	2 (10.5)	15(78.9%)	4(21.1%)	19
6	0	2 (100)	2(100%)	0	2

4-6 Week Post-Therapy Outcome by Duration of IV Dosing--Sponsor Evaluable Patients

Days IV Dosing	Cure	Failure	Total
2	19(95%)	1(5%)	20
3	24(82.8%)	5(17.2%)	29
4	14(87.5%)	2(12.5%)	16
5	13(76.5%)	4(23.5%)	17
6	3(100%)	0	3

Clinical outcome at 10-14 days post-therapy by baseline pathogen among the 84 patients that were considered evaluable by the sponsor at this visit.

	Number of Patients (% of Pathogen Total)				
Pathogen	Total	Cured	Improved	Cure + Improvement	Failure
Streptococcus pneumoniae	31	23 (74.2)	5 (16.1)	28(90.32)	3(9.68)
Haemophilus influenzae	23	15 (65.2)	5 (21.7)	20(86.96)	3(13.04)
Staphylococcus aureus	4	2	2	3	1
Moraxella catarrhalis	6	3	3	6(100)	0
Mycoplasma pneumoniae	2	2	0	2(100)	0
Klebsiella pneumoniae	1	0	0	0	1(100)
Enterobacter cloacae	1	0	0	0	1(100)

MO Note: Patients with more than one pathogen at baseline are listed once for each pathogen identified. Patients infected with Mycoplasma pneumoniae are listed on the basis of clinical characteristics only. Patients with positive mycoplasma culture and/or serology are listed in the next table.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients With Evidence of Infection With Mycoplasma Pneumoniae.

		Number of Patients (% of Category Total)			
Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
Culture Only	1	1	0	1	0
Culture + IgG	1	1	0	1	0
IgM Only	6	4	2	6	0
IgG Only	1	0	1	1	0
Total Patients With Evidence of Infection	9	6	3	9	0

MO Note: Culture = isolation of organism with PCR confirmation. IgM titer >=10, IgG >= four fold rise in titer from baseline.

Clinical outcomes at 10-14 Days Post-Therapy for Patients With Evidence of Infection With *Chlamydia pneumoniae.*

		Number of Patients (% of Category Total)			
Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
IgG Only	19	10 (52.6)	7 (36.8)	17(89.5)	2(10.5)
IgM + IgG	2	0	2	2	0
Total Patients with Evidence of Infection	21	10 (47.6)	9 (42.9)	19(90.5)	2(9.5)

MO Note: Infection was based on IgM >=20, IgG > 512, or >= 4-fold rise in titer from baseline.

Clinical Outcomes at 10-14 Days Post-Therapy for Patients with Evidence of Infection With Legionella--Sponsor Evaluable Patients

Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
IgG	12	4 (33.3)	6 (50)	10(83.3)	2(16.7)

MO Note: Evidence of infection was based on a 4-fold rise in IgG from baseline.

MO Note on Atypical Pathogen Patients: Serology was the primary objective criteria used for defining infection with an atypical pathogen. The medical officer asked the sponsor to separate the data on these patients from the rest of the application so that an depth review could be performed. Patients were reviewed to assess clinical, radiographic and laboratory parameters. All patients had radiographic evidence of pneumonia. Upon review, the medical officer found

that the patients' clinical criteria was consistent with a diagnosis of atypical pneumonia. For example, the majority of patients infected with Mycoplasma pneumoniae (7 out of 11, 64%) were between the ages of 17 and 36. (The majority of patients were recruited from millitary clinics.) Patients infected with Legionella pneumophila had other clinical evidence, in addition to positive serology, that would be consistent with infection. For example, 4 of 15 (27%) had unexplained hyponatremia. Hyponatremia is significantly more associated with Legionella infection than with pulmonary infections of other etiologies (Mandell, et al Principles and Practice of Infectious Diseases, Third edition page 1769).

The clinical outcomes at 4-6 weeks by baseline pathogen, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella were similar to the results seen at the 10-14 day post-therapy visit. Therefore, those tables will not be reproduced here.

Bacteriological outcomes (1) by baseline pathogens among the bacteriologically evaluable patients at the final visit (4-6 weeks post-therapy) --Sponsor Evaluable Patients in Study 0625, Azithromycin Arm

	Number of Patients(% of Pathogen Total)		
Pathogen	Total	Eradication	Persistence
Streptococcus pneumoniae	36	34 (94.4)	2 (5.6)
Haemophilus influenzae	27	26 (96.3)	1 (3.7)
Staphylococcus aureus	5	5	0
Moraxella catarrhalis	7	6 (85.7)	1 (14.3)
Mycoplasma pneumoniae	2	2	0
Klebsiella pneumoniae	1	0	1
Enterobacter cloacae	1	0	1

(1) 79 Pathogens isolated from 66 bacteriologically evaluable patients.

Medical Officer's Efficacy Results

Evaluable patients were reviewed for appropriateness of inclusion. No changes were made in this population from the sponsor's analysis. Non-evaluable patients were reviewed. The most frequent reason for exclusion from an evaluable analysis was failure to detect a baseline pathogen (32%). No changes were made from the non-evaluable population. As in study 618, failures were carried forward by the sponsor even if these patients had a follow-up visit that fell outside the specified window. The medical officer reviewed these patients and confirmed their appropriate inclusion or exclusion from the analyses. Therefore, the sponsor's numbers are considered valid and the table is repeated below for reference.

CLINICAL OUTCOMES--SPONSOR EVALUABLE PATIENTS

Clinical Outcome	10-14 Day Post-Therapy	4-6 Week Post-Therapy
Cured	50 (59.5)	73 (85.9)
Improved	24 (28.6)	N/A
Cured + Improved	74 (88.1)	N/A
Failure	10(11.9)	12 (14.1)

MO Note on Bacteremic Patients: Nine patients had a positive blood culture; 8 of 9 (89%) were cured, while 1 (11%) failed treatment. All had Streptococcus pneumoniae.

Subgroup analysis of azithromycin IV efficacy for treatment of CAP in sponsor's and medical officer's evaluable patients enrolled in protocol 0625.

Subgroup	n cured or improved / N evaluable	% cured or improved	p-value CMH
Female	25 / 28	89%	0.813
Male	49 / 56	88%	
< 45	19 / 21	90%	0.277
45-65	19 / 24	79%	
>65	36 / 39	92%	
white	43 / 50	86%	0.337
black	23 / 24	96%	
other	8 / 10	80%	
Days on IV			
2 days	20 / 20	100%	0.258
3 days	25 / 30	83%	
4 days	12 / 13	92%	
5 days	15 / 19	79%	
6 days	2 / 2	100%	

Safety

Summary of Adverse Events for study 0625 (1) by body system – All treated patients

	Number of Patients (2) with an adverse event (% of safety evaluable)
	Azithromycin
Number of Patients	
Evaluable for safety	212 (100.0%)
With adverse event	181 (85.4%)
Discontinued due to adverse event (3)	13 (6.1%)
Adverse Events by Body Systems	
body as a whole	102 (48.1%)
cardiovascular	30 (14.2%)
digestive	88 (41.5%)
endocrine	1 (0.5%)
hemic and lymphatic	14 (6.6%)
metabolic and nutritional	55 (25.9%)
skin and appendages	15(7.1%)
musculoskelatal	12 (5.7%)
nervous	61 (28.8%)
respiratory	57 (26.9%)
special senses	14 (6.6%)
urogenital	19 (9.0%)

(1) Adverse events which occurred within 35 days post-therapy or at any time while patient was on study (whichever was the latest observation).
(2) Patients counted once within each body system for multiple adverse events within the same body system.
(3) Number of patients who discontinued due to adverse events or laboratory abnormality.

Stat Note: A statistically significantly higher percent of patients reported experiencing one or more adverse events in the metabolic and nutritional system when treated with azithromycin in the open protocol 0625 than those treated with azithromycin under the comparative protocol 0618 (p-value < 0.0001). The percents of patients experiencing one or more adverse events were 25.9% (55/212) and 9.4% (19/202) for protocols 0625 and 0618, respectively.

Table: Incidence of adverse events greater than or equal to 1% for all treated patients for protocol 0625 in descending sequence by percent of the azithromycin-treated patients

System	Adverse Experiences	Azithromycin IV N = 212	Azithromycin IV%
Nervous	insomnia	30	14.2%
Body	headache	27	12.7%
Digestive	nausea	25	11.8%
Digestive	diarrhea	24	11.3%
Body	abdominal pain	23	10.8%
Digestive	constipation	22	10.4%
Metabolic and nutritional	hypokalemia	20	9.4%
Body	injection site reaction - pain	18	8.5%
Body	chest pain	13	6.1%
Body	injection site reaction - device complication	13	6.1%
Digestive	vomiting	13	6.1%
Metabolic and nutritional	peripheral edema	12	5.7%
Body	back pain	11	5.2%
Body	pain	11	5.2%
Metabolic and nutritional	electrolyte abnormality	11	5.2%
Digestive	dyspepsia	10	4.7%
Hemic and Lymphatic	anèmia	10	4.7%
Nervous	anxiety	9	4.2%
Body	injection site reaction - infect/inflam	8	3.8%
Digestive	liver function tests abnormal	8	3.8%
Musculoskeletal	arthralgia	8	3.8%
Respiratory	pneumonia	8	3.8%
Respiratory	rhinitis	8	3.8%
Cardiovascular	congestive heart failure	7	3.3%
Digestive	flatulence	7	3.3%
Nervous	dizziness	7	3.3%
Respiratory	pleural effusion	7	3.3%
Respiratory	respiratory disorder	7	3.3%
Skin and skin structures	rash	7	3.3%
Urogenital	urinary tract infection	7	3.3%
Cardiovascular	tachycardia	6	2.8%
Metabolic and nutritional	edema	6	2.8%
Respiratory	dyspnea	6	2.8%
Respiratory	pharyngitis	6	2.8%
Metabolic and nutritional	SGPT increased	5	2.4%
Respiratory	asthma	5	2.4%
Respiratory	epistaxis	5	2.4%
Respiratory	hypoxia	5	2.4%
Skin and skin structures	pruritus	5	2.4%
Special senses	conjunctivitis	5	2.4%
Metabolic and nutritional	gout	4	1.9%
Metabolic and nutritional	SGOT increased	4	1.9%
Nervous	agitation	4	1.9%
Urogenital	urinary incontinence	4	1.9%
Cardiovascular	myocardial infarction	3	1.4%
Metabolic and nutritional	hyperglycemia	3	1.4%
Nervous	confusion	3	1.4%
Nervous	depression	3	1.4%
Nervous	somnolence	3	1.4%
Respiratory	bronchitis	3	1.4%
Respiratory	cough increased	3	1.4%
Respiratory	hemoptysis	3	1.4%
Respiratory	pleural disorder	3	1.4%
Skin and skin structures	sweating	3	1.4%
Special senses	dry eyes	3	1.4%

Supportive Studies

The sponsor submitted 3 non-U.S. studies to support the use of intravenous/oral azithromycin in patients with pneumonia. A table providing an overview of these studies follows.

Protocol #	Study Design	Treatment	Number treated (Number Entered)	Age Range (Mean)
066-349 Countries: Australia, Poland, Italy, Norway, U.K., Sweden, Finland	Open, multicenter, randomized, comparative	Azithromycin 500mg IV for 2-5 days, followed by 500mg PO for 5 days vs. Penicillin G 600mg IV q6h (3 gms t.i.d. in Sweden) or IM (300-600mg b.i.d.) And amoxicillin 500mg t.i.d. (penicillin 1gm PO t.i.d. in Sweden) with erythromycin 500mg IV or PO q.i.d. for patients with atypical pneumonias.	98 (98) 98 (98)	18-86 (54.8) 16-94 (53.5)
066-350 Countries: Belgium, Finland, Germany, Netherlands, U.K.	Open, multicenter, randomized, comparative	Azithromycin 500mg IV for 2-5 days, followed by 500mg PO for 5 days vs. Cefuroxime, 750mg IV q8h for 2-7 days, then 500mg PO q12h to day 10. Plus Erythromycin 500mg (IV or PO) q.i.d. for 14 days for patients with suspected atypical pathogens.	92 (94) 97 (97)	18-92 (53.8) 18-92 (53.0)

066-359 Countries: Australia, New Zealand	Open label, noncomparative, multicenter	Azithromycin 500mg IV q.d. for 2-5 days followed by 250mg PO for total duration of 7-10 days.	99 (99)	19-91 (61.1)

MO Note: Two investigators from study 349, one from Australia and one from the U.K., also enrolled patients in studies 350 and 359.

Clinical efficacy rates for the supportive studies are noted in the following table.

MO Note: The primary efficacy analysis for the three studies is an end of treatment (14 day) intent-to-treat analysis. No post-therapy assessments were made.

Study Number	14 Day ITT Efficacy Rate Azithromycin	14 Day ITT Efficacy Rate Comparator
006-349	84/95 (88%)	77/93(83%)
006-350	72/87 (82.8%)	78/89 (87.6%)
006-359	85/96 (89%)	N/A

Bacteriological eradication rates for pathogens are listed in the following table. These are also based on day 14 ITT results.

Study 006-349 Organism	Eradication Rate Azithromycin	Eradication Rate Comparator
Streptococcus pneumoniae	26/27 (96%)	19/21 (91%)
Haemophilus influenzae	6/7	6/8
Staphylococcus aureus	0/1	4/4
Chlamydia pneumoniae	3/3	3/4
Mycoplasma pneumoniae	8/9	10/11
Legionella pneumophila	2/4	3/3

Study 006-350 Organism	Eradication Rate Azithromycin	Eradication Rate Comparator
Streptococcus pneumoniae	12/18 (66.7%)	16/18 (88.9%)
Haemophilus influenzae	9/10	6/7
Staphylococcus aureus	1/2	2/2
Mycoplasma pneumoniae	9/10	8/8
Legionella pneumophila	1/1	1/1
Chlamydia pneumoniae	2/2	3/3

Study 006-359 Organism	Eradication Rate Azithromycin
Streptococcus pneumoniae	10/10 (100%)
Haemophilus influenzae	10/11
Mycoplasma pneumoniae	5/5
Legionella pneumophila	4/4
Chlamydia psittaci	7/7

MO Note: The above studies are not considered fully supportive by this reviewer for the following reasons:

- *Efficacy was based on an end of treatment assessment. No post-therapy assessments were made. At best, one can consider the eradication rates as presumptive.*
- *Two investigators participated in all three studies. These sites should be part of one study, not all three.*

Summary of Bacteriological Efficacy from Pivotal CAP Trials:

Bacteriological outcomes (1) by baseline pathogens among the bacteriologically evaluable patients at the final visit (4-6 weeks post-therapy) --Sponsor Evaluable Patients, Azithromycin-treated.

Number of Patients(% of Pathogen Total)

Pathogen	Total	Eradication	Persistence
Streptococcus pneumoniae	67	64 (95.5)	3 (4.5)
Haemophilus influenzae	43	41 (95.3)	2 (4.7)
Staphylococcus aureus	10	9	1
Moraxella catarrhalis	10	9	1
Mycoplasma pneumoniae	5	4	1
Bordetella bronchiseptica	1	1	0
Klebsiella pneumoniae	1	0	1
Legionella pneumophila	1	1	0
Enterobacter cloacae	1	0	1

(1) 139 Pathogens isolated from 119 bacteriologically evaluable patients.

Presumed Bacteriological Outcomes at 10-14 Days Post-Therapy for Patients Treated with Azithromycin With Evidence of Infection with Atypical Pathogens for Studies 0618 and 0625

		Number of Patients (% of Category Total)			
Evidence of Infection	Total	Cure	Improvement	Cure + Improvement	Failure
Mycoplasma pneumoniae	18	11 (61%)	5 (28%)	16 (89%)	2 (11%)
Chlamydia pneumoniae	34	15 (44%)	13 (38%)	28 (82%)	6 (18%)
Legionella pneumophila	16	5 (31%)	8 (50%)	13 (81%)	3 (19%)

U.S. Phase III CAP Safety Data

Number of Patients Treated

Safety data were available for 615 patients; 414 patients received azithromycin and 201 patients received an active comparative agent in two U.S. adult IV clinical trials for CAP:

Numbers of Patients Treated in U.S. Phase III Studies	
Treatment	Combined Studies
Azithromycin:	414
Comparative Agent: Cefuroxime[a]	201
TOTAL	615

a: Included optional erythromycin.

Extent of Exposure:

For all azithromycin patients, the mean duration of treatment was 3.3 days for IV therapy and 7.9 days for all therapy (i.e., IV plus oral therapy). In the comparative studies, for azithromycin and comparative agent, the mean duration of treatment was 3.4 and 4.0 days for IV therapy, respectively, and 7.6 and 9.2 days for all therapy, respectively.

Table: Incidence of adverse events greater than or equal to 1% for all treated patients for CAP protocols 0618 & 0625 in sequence by body system of the azithromycin-treated patients

System	Adverse Experiences	Azithromycin IV N = 414	Azithromycin IV%
Body	abdominal pain	33	8.0%
	asthenia	4	1.0%
	back pain	21	5.1%
	chest pain	25	6.0%
	death	4	1.0%
	fever	10	2.4%
	headache	62	15.0%
	injection site reaction - infect/inflam	26	6.3%
	injection site reaction - pain	34	8.2%
	injection site reaction - device complication	24	5.8%
	pain	22	5.3%
	sepsis	4	1.0%
Cardiovascular	angina pectoris	7	1.7%
	arrhythmia	4	1.0%
	congestive heart failure	11	2.7%
	hypertension	9	2.2%
	myocardial infarction	5	1.2%
	tachycardia	6	1.4%
Digestive	anorexia	4	1.0%
	constipation	51	12.3%
	diarrhea	44	10.6%
	dyspepsia	22	5.3%
	flatulence	9	2.2%
	gastritis	4	1.0%
	liver function test abnormal	9	2.2%
	nausea	45	10.9%
	oral moniliasis	5	1.2%
	vomiting	26	6.3%
Hemic and Lymphatic	anemia	14	3.4%
Metabolic and nutritional	edema	11	2.7%
	electrolyte abnormality	11	2.7%
	hypokalemia	25	6.0%
	peripheral edema	14	3.4%
	SGOT increased	5	1.2%
	SGPT increased	5	1.2%
Musculoskeletal	arthralgia	16	3.9%
	bone disorder	4	1.0%
Nervous	agitation	10	2.4%
	anxiety	24	5.8%
	confusion	7	1.7%
	depression	4	1.0%
	dizziness	13	3.1%
	insomnia	57	13.8%
	somnolence	5	1.2%
Respiratory	asthma	10	2.4%
	bronchitis	7	1.7%
	cough increased	6	1.4%
	dyspnea	16	3.9%
	epistaxis	11	2.7%
	hemoptysis	5	1.2%
	hypoxia	7	1.7%
	pharyngitis	11	2.7%
	pleural disorder	6	1.4%
	pleural effusion	16	3.9%
	pneumonia	22	5.3%
	respiratory disorder	25	6.0%
	rhinitis	16	3.9%
	sinusitis	5	1.2%
Skin and skin structures	pruritus	6	1.4%
	rash	13	3.1%
	skin disorder	4	1.0%
	skin ulcer	4	1.0%
Special senses	conjuntivitis	5	1.2%
	taste perversion	4	1.0%
Urogenital	urinary incontinence	5	1.2%
	urinary tract infection	8	1.9%

Demographic characteristics are summarized by treatment group in the table below. The greatest proportion of patients in all three patient groups were white, males, and 65 years of age.

Demographic Characteristics - All Treated Patients in U.S. CAP Phase III Studies			
Demographic Characteristic	Azithromycin[a] N (%)	Azithromycin[b] N (%)	Comparative Agents[c] N (%)
Total No. of Patients	414	202	201
Sex			
Male	261 (63.0)	125 (61.9)	127 (63.2)
Female	153 (37.0)	77 (38.1)	74 (36.8)
Age (years)			
16-44	111 (26.8)	51 (25.2)	51 (25.4)
45-64	115 (27.8)	59 (29.2)	58 (28.9)
65	188 (45.4)	92 (45.5)	92 (45.8)
Mean Age	58.17	58.87	58.53
Age range	17-95	19-94	18-93
Race			
White	262 (63.3)	143 (70.8)	149 (74.1)
Black	121 (29.2)	47 (23.3)	47 (23.4)
Other[d]	31 (7.5)	12 (5.9)	5 (2.5)

a: Includes Studies 93CE33-0618 and 93CE33-0625
b: Includes Study 93CE33-0618 only
c: Comparative treatment consisted of IV cefuroxime followed by oral cefuroxime with optional IV or oral erythromycin.
d: Other includes Biracial. Hispanic, Indian, Latino, Oriental, and unknown.

Adverse Reactions During IV Therapy

A total of 66.4% (275/414) of all azithromycin patients in the U.S. Phase III CAP studies reported at least one adverse event of all causality during IV therapy only.

Among azithromycin patients, the most frequently reported adverse events included insomnia (9.9%, 41/414), headache (9.4%, 39/414), constipation (8.0%, 33/414), insertion site pain (7.7%, 32/414), nausea (7.0%, 29/414) insertion site device complication (5.3%, 22/414), and insertion site infection/inflammation (4.8%, 20/414). The majority of adverse events of all causalities were of mild or moderate intensity as reported by the sponsor.

MO Note: A listing of death narratives is provided as Attachment A at the end of this review.

Indication #2: Pelvic Inflammatory Disease (PID)

Introduction (The following is excerpted from the CDC guidelines on sexually transmitted diseases)

PID (Pelvic Inflammatory Disease) comprises a spectrum of inflammatory disorders of the upper genital tract among women and may include any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in the majority of cases; however, microorganisms that can be part of the vaginal flora, such as anaerobes, *G. vaginalis, H. influenzae,* enteric Gram-negative rods, and *Streptococcus agalactiae* also can cause PID. Some experts also believe that *M. hominis* and *U. urealyticum* are etiologic agents of PID.

Proposed Package Insert:

MO Note: A revised INDICATIONS AND USAGE section of the label was proposed by the sponsor on December 17, 1996. It now reads,

The sponsor submitted two non-US studies, 066-341 and 066-342, in support of this indication.

Trial #1: Protocol 066-341

Title: A MULTICENTER OPEN COMPARATIVE 3-WAY RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF IV AND ORAL AZITHROMYCIN IN COMPARISON WITH DOXYCYCLINE, CEFOXITIN, PROBENECID AND METRONIDAZOLE IN THE TREATMENT OF PATIENTS WITH ACUTE PELVIC INFLAMMATORY DISEASE

Study Dates: April 2, 1991 - September 24, 1993

Countries participating in the trial:

Finland (centers 227,228,229,230), Germany (centers 210, 222, 311, 324,433), Norway (centers 192, 193, 194, 195, 196, 197, 198, 199), Sweden (center 116), UK (centers 180, 181, 183, 184, 234)

Methods

Study Objective: To compare the efficacy and safety of azithromycin (initially given parenterally, then orally) and azithromycin with metronidazole against doxycyline with metronidazole, cefoxitin and probenecid (comparative regimen) in the treatment of patients with acute pelvic inflammatory disease.

Study Design:

This was an open label, 3-way comparative, multicenter study in patients with acute pelvic inflammatory disease. The diagnosis was to be confirmed by laparoscopy whenever possible.

Patients giving informed consent were to be randomly assigned in equal numbers to the following three treatment groups, after stratification for severity of illness:

1. Azithromycin 500 mg iv once daily for 1 day, then 250 mg orally once daily for 6 days.

2. Azithromycin as in group 1 with concomitant metronidazole, either 500 mg iv q 8h for the first day followed by 400 mg oral q8h for 11 days or 400mg oral q8h for 12 days.

3. Metronidazole 500 mg iv q8h for the first day followed by metronidazole 400 mg orally q8h for 11 days (or 400 mg orally q8h for 12 days) with concomitant doxycycline 100 mg q12h orally for 14 days and cefoxitin 2g iv or im and probenecid 1g orally on the first day.

MO Comment: There is no anaerobic coverage in the first arm. The third arm has two agents with activity against anaerobes (metronidazole and cefoxitin). The cefoxitin is needed for gram negative and Neisseria coverage. According to the MMWR (CDC recommendations) treatment guidelines on sexually transmitted diseases treatment for PID should be directed toward multiple organisms, including anaerobes. Cefoxitin is indicated for the treatment of gynecological infections including pelvic inflammatory disease.

Patients were to be hospitalized; clinical assessments were to be made before treatment, on the second day of treatment, between the 7th and 9th days of treatment, at the end of treatment (day 15-18) and at follow-up assessment 35 to 40 days after the start of treatment. Bacteriological assessments were to be made before treatment, at the end of treatment and at the follow-up visit. Endometrial sampling was to be performed before treatment and at follow-up.

Inclusion Criteria:

- Female patients, aged 18 years or older, fulfilling the following criteria:

Mandatory for diagnosis: abdominal direct tenderness (with or without rebound tenderness); tenderness with motion of the cervix and uterus; adnexal tenderness.

Plus

One or more of the following were necessary for diagnosis: Gram's stain of the endocervix was positive for diplococci; temperature was greater than 38°C; leukocytosis > $10^4/mm^3$; purulent material with white blood cells present obtained from peritoneal cavity by culdocentesis or laparoscopy; pelvic abscess or inflammatory complex on bi-manual exam or by sonography; Chlamydia in endometrium or endocervix (detected by antigen or culture); laparoscopic signs of tubal inflammation (erythema and or edema, or evidence of hydrosalpinx).

MO Comment: The above criteria are those of Hager WD, Eschenbach DA, Spence MR, Sweet RL. Criteria for diagnosis and grading of salpingitis [editorial]. Obstet Gynecol 1983;61:113-4.

Exclusion Criteria:

- Patients who were terminally ill, immunosuppressed or thought ot have any underlying disease that would interfere with evaluation of the terapeutic response.
- Patients with known allergy to macrolides, penicillin, tetracyclines, metronidazole, cephalosporins, or probenecid.
- Pregnant or breast-feeding women.
- Patients who received antibiotic therapy within 2 weeks of beginning the study.
- Patients with liver function test results greater than 1.5 x upper limit of normal.
- Patients with renal impairment or failure (creatinine clearance < 40ml/min or serum creatinine > 130 micromoles/l).
- Patients requiring concomitant antimicrobial therapy.
- Patients with concomitant infections that may confuse interpretation of the results of study treatment.
- Patients with malabsorption.
- Patients with palpable tubo-ovarian abscess.

- Drug addicts, alcoholics or those taking recreational drugs.
- Patients taking oral hypoglycemics, ergot, dicoumarin anticoagulants, carbamazepine, cyclosporins, digoxin or theophylline.
- Patients who entered the study before.

Efficacy

The main analyses undertaken were intent to treat (ITT) analyses. The clinical response used was the investigator's assessment at the end of treatment visit. An evaluable patient analysis was performed.

Bacteriological response, correlated with clinical response, was tabulated by pathogen and treatment group for pathogens recorded at baseline. Pathogens were divided into "key pathogens" and "non-key pathogens." The definitions of key pathogens were as follows:

Key Site	Key Pathogens
Endocervix	*Neisseria gonorrhea, Chlamydia trachomatis* and *Mycoplasma species*
Endometrium	Any Organism Isolated
Fimbrial brushings	Any organism isolated that was considered
Peritoneal fluid	pathogenic by the investigator.

The following outcomes were defined for the end of treatment visit:

Eradicated	Disappearance of the baseline pathogen. If a sample was not taken at the end of treatment from a site that was positive at baseline and the pathogen was not isolated from any other key site, then the pathogen was presumed eradicated in the ITT analysis.
Persisted	Persistence of the key pathogen at one or more key sites.
Superinfection	Pathogen isolated that was not present at baseline.

To be included in the bacteriological ITT analysis, patients had to have a key pathogen isolated from a key site at baseline and a sample from one or more of the key sites between Days 1 and 28 inclusive or a positive Chlamydia antigen test at baseline. To be included in the bacteriological evaluable analysis, patients who had a laparoscopy at baseline had to have a sample taken from a key site at baseline and between Days 9 and 21 inclusive. Patients who had no laparoscopy at baseline had to have samples taken from the endometrium at baseline and between Days 9 and 21 inclusive.

The following criteria were used to exclude data from the end of treatment analyses:

X = patient excluded from analysis. I = patient included in analysis.

Evaluable Patient Analysis (ITT Patient Analysis)

Criterion	Clinical	Bacteriological
1. No key pathogen isolated in baseline window	X(I)	X (X)
2. Resistant pathogen at baseline	X(I)	X(I)
3. No susceptibility testing against the baseline pathogen(s)	X(I)	X(I)
4. Inappropriate primary diagnosis	X(X)	X(X)
5. Previous antibacterial treatment within 2 weeks of start of study treatment	X(I)	X(I)
6. Concomitant anti-bacterial treatment	see note 1	see note 1
7. No clinical signs/symptoms recorded at baseline	X(X)	I(I)
8. Patient entered into the study more than once	X(X)	X(X)
9. Missing data and data outside of windows	see note 2	see note 2
10. Inadequate exposure to study drug	X(I)	X(I)
11. Unprotected sexual intercourse	X(I)	X(I)

Note 1: Patients who received systemic antibacterial therapy that was concomitant with their study treatment and started with or before study drug were considered clinically and bacteriologically unevaluable (evaluable and ITT analysis). Patients who started additional antibiotic therapy after the first day of study treatment were considered clinical failures unless assessments made at the time of or prior to the introduction of the additional treatment indicated otherwise or the concomitant therapy would have had no effect on the response (e.g. topical preparations).

- *MO note: These patients were reviewed carefully to ensure that they were not failing therapy.*

If a patient received additional antibacterial therapy due to an inadequate response they were regarded as a clinical failure. If no samples were taken before the switch to alternative therapy, the patient was considered bacteriologically unevaluable (evaluable and ITT) as the use of clinical response to determine eradication or persistence is inappropriate for PID studies.

- *MO note: Indeed, the 1992 Guidelines for Acute Pelvic Inflammatory Disease state, "The*

microbiological result is the most important determinant of outcome. The presence of N. gonorrhea or C. trachomatis, even in the absence of symptoms, is indicative of a failure of treatment..."

Note 2: If no clinical assessments were made after baseline, the patient was excluded from the clinical evaluable and ITT analyses. To be included in the evaluable analysis the patient had to have a visit between Days 9 and 21. If no samples were taken from any of the key sites after baseline, the patient was excluded from the bacteriological evaluable and ITT analyses.

- *MO note: If a patient had a visit before Day 9, she could still be included in the evaluable analysis if there were evidence of treatment failure.*

Drug Administration

Adequate exposure to the study drug was defined as intravenous treatment on the first day (one dose) plus at least 50% of the planned oral treatment.

Sponsor's Efficacy Results

Patient Evaluation Groups

Evaluation	Azithromycin	Azithromycin/Metronidazole	Comparative
Randomized	76	80	72
Received Treatment	76	80	72
Discontinued Rx	5	6	9
Completed Rx	71	74	63
EFFICACY ANALYSES:			
Clinical Response			
-Intent-to-treat day 15-18	*73*	*79*	*69**
-Evaluable at day 15-18	29	31	26
Bacteriological Response			
-Intent-to-treat day 15-18	*36*	*46*	*40**
-Evaluable at day 15-18	26	27	24
SAFETY ANALYSES			
Adverse Experience	76	80	72
Laboratory Data	66	72	66

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*These will be the primary analyses reported both for the sponsor's analysis and the MO analysis. The IDSA guidelines state that "...the microbiological result is the most important determinant of outcome. The presence of *N. gonorrhoeae* and *C. trachomatis,* even in the absence of symptoms, is indicative of a failure of treatment" Further, it is recommended that the microbiological outcome should be determined 2-4 days after the completion of therapy.

Demographic Note: The study population was homogenous with respect to demographic characteristics. It was 100% female. The majority of patients were age 18-44 with 96% (73/76) in the azithromycin arm, 99% (79/80) in the azithromycin/metronidazole, and 93% (67/72) in the comparator arm. The majority of the patients were white with 91% (69/76) in the azithromycin arm, 87.5% (70/80) in the azithromycin/metronidazole, and 87.5% (63/72) in the comparator arm.

Sponsor's Reasons for Exclusion from Clinical Evaluable Analysis at Day 15-18

	TREATMENT GROUP		
Reason for Exclusion	Azithromycin	Azithromycin/ Metronidazole	Comparative
No baseline culture or pathogen isolated	37	36	31
Resistant pathogen	0	0	1
No susceptibility test at baseline	5	9	7
Inappropriate diagnosis	1	0	0
Concomitant antibacterial Rx	0	0	2
Inadequate exposure to study drug	1	0	0
Missing data or data outside of window	3	3	3
Unprotected Sex	0	1	2
Total unevaluable	47	49	46

Sponsor's reasons for exclusion from clinical intent to treat analysis at day 15-18

	TREATMENT GROUP		
Reason for exclusion	Azithromycin	Azithromycin/ Metronidazole	Comparative
Incorrect diagnosis	1	1	0
No signs/symptoms recorded pre-treatment	0	0	1
Missing data or data outside of window	2	0	2
Total Unevaluable	3	1	3

Sponsor's reasons for exclusion from bacteriological evaluable analysis at day 15-18

	TREATMENT GROUP		
Reason for exclusion	Azithromycin	Azithromycin/ Metronidazole	Comparative
No baseline culture or no pathogen isolated	37	36	31
Resistant Pathogen	0	0	1
No susceptibility test at baseline	5	9	7
Incorrect diagnosis	1	0	0
Concomitant antibacterial treatment	1	0	3
Inadequate exposure to study drug	1	0	0
Missing data or data outside of window	5	7	4
Unprotected sexual intercourse	0	1	2
Total unevaluable	50	53	48

Sponsor's reasons for exclusion from bacteriological intent to treat analysis at day 15-18.

	TREATMENT		
Reason for exclusion	Azithromycin	Azithromycin/ Metronidazole	Comparative
No baseline culture or no pathogen isolated	36	30	28
Inappropriate primary diagnosis	1	0	0
Concomitant antibacterial treatment	1	1	3
Missing data or data outside of window	2	3	1
Total unevaluable	40	34	32

Note on Demographics: The overwhelming majority of the patients entered were white with a mean age of 27.9 years (range 18-54).

Number of Patients Enrolled by Center for Study 341:

	Azithromycin		Azithromycin/Metronidazole		Comparative	
Center	Randomized	Received Treatment	Randomized	Received Treatment	Randomized	Received Treatment
116	1	1	0	0	0	0
180	0	0	1	1	0	0
181	1	1	2	2	2	2
183	9	9	8	8	9	9
184	0	0	1	1	0	0
192	2	2	3	3	2	2
193	6	6	7	7	8	8
194	1	1	3	3	2	2
195	3	3	3	3	1	1
196	0	0	1	1	0	0
197	5	5	5	5	5	5
198	4	4	3	3	3	3
199	1	1	2	2	0	0
210	2	2	2	2	2	2
222	2	2	2	2	2	2
227	2	2	3	3	4	4
228	4	4	4	4	4	4
229	2	2	2	2	3	3
230	4	4	3	3	3	3
234	11	11	10	10	8	8
311	10	10	11	11	10	10
324	4	4	4	4	4	4
433	2	2	0	0	0	0
Total	76	76	80	80	72	72

Overall Summary of Sponsor's Efficacy Results: (Patients included those with and without bacteriological assessments at end of therapy). Included are the cure rates by treatment and 95% confidence intervals of the difference in treatment cure rates for the sponsor's evaluable populations using both ITT at 15 days post-therapy and LOCF analysis for the long term visit.

	Azithromycin	Azithromycin/ Metronidazole	Comparator*
Day 15 ITT			
Cured	59/73 (80.8%)	58/79 (73.4%)	53/69 (76.8%)
Improved	11/73 (15.1%)	19/79 (24.1%)	13/69 (18.8%)
Clinical Success (cured or improved)	70/73 (95.9%)	77/79 (97.5%)	66/69 (95.7%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	-1.6% (-8.6% , 5.5%)		
Azi - Comparator	0.2% (-7.8% , 8.3%)		
Azi/Metro - Comparator	1.8% (-5.5% , 9.1%)		
At Long Term Follow-up Visit (Last Observation Carried Forward)			
Cured	62/74 (83.8%)	69/79 (87.3)	56/69 (81.2%)
Improved	7/74 (9.5%)	8/79 (10.1%)	6/69 (8.79%)
Clinical Success (cured or improved)	69/74 (93.2%)	77/79 (97.5%)	62/69 (89.9%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	-4.2% (-12.2% , 3.8%)		
Azi - Comparator	3.4% (-7.1% , 13.9%)		
Azi/Metro - Comparator	7.6% (-1.7% , 16.9%)		

*Comparative treatment consisted of metronidazole 500 mg iv q8h for the first day followed by metronidazole 400 mg orally q8h for 11 days (or 400 mg orally q8h for 12 days) with concomitant doxycycline 100 mg q12h orally for 14 days and cefoxitin 2 g iv or im stat and probenecid 1 g orally stat on the first day.

MO Note: Of the 221 end of treatment ITT population, 184 (83%) had a baseline laparoscopy. Sixty-two, 68, and 54 had laparoscopy among the patients in each treatment arm above.

Stat Note: Based upon DAIDP's Points to Consider, azithromycin alone could be considered therapeutically inferior to the azithromycin/metronidazole combination in the LOCF analysis because

the lower bound of the 95% confidence interval is lower than -10%. Otherwise, the treatments would be considered therapeutically comparable.

Summary of Sponsor's Bacteriological and Clinical Response for the Pathogens listed in the January 13, 1997 Proposed Package Insert.

Day 15 ITT Analysis

Pathogen	Azithromycin				Azithromycin/Metro				Comparative			
	Bact response		Clinical Response		Bact response		Clinical Response		Bact response		Clinical Response	
	E	P	C	F	E	P	C	F	E	P	C	F
Chlamydia trachomatis	14	0	14	0	20	0	20	0	24	0	24	0
N. gonorrhoeae	4	0	4	0	5	0	5	0	4	0	4	0
Mycoplasma hominis	8	2	10	0	12	3	15	0	7	2	9	0

E = Eradicated
P = Persisted
C = Cure
F = Failure

Medical Officer's Efficacy Results

MO Comment:

Review of the data disclosed seven patients with persistent pathogens at the end of therapy. According to the IDSA Guidelines for Pelvic Inflammatory Disease, such patients despite clinical improvement should still be considered failures. As a result, these patients are considered failures at end of therapy. They will also be carried forward and considered failures in the LOCF analysis. These patients all had Mycoplasma hominis as the persistent pathogen. Of the seven patients, two were in the azithromycin arm, three in the azithromycin/metronidazole arm, two in the comparative arm.

Cure rates by treatment and 95% confidence intervals of the difference in treatment cure rates for the medical officer's evaluable populations using ITT population at 15 days post-therapy and using the LOCF for the long term follow-up visit.

	Azithromycin	Azithromycin/ Metronidazole	Comparator
Day 15 ITT			
Cured	57/73 (78.1%)	55/79 (69.6%)	51/69 (73.9%)
Improved	11/73 (15.1%)	19/79 (24.1%)	13/69 (18.8%)
Clinical Success (cured or improved)	68/73 (93.2%)	74/79 (93.7%)	64/69 (92.8%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	-0.5% (-9.7% , 8.7%)		
Azi - Comparator	0.4% (-9.4% , 10.2%)		
Azi/Metro - Comparator	0.9% (-8.6% , 10.4%)		
At Long Term Follow-up Visit (Last Observation Carried Forward)			
Cured	61/74 (82.4%)	66/79 (83.5%)	55/69 (79.7%)
Improved	7/74 (9.5%)	8/79 (10.1%)	6/69 (8.7%)
Clinical Success (cured or improved)	68/74 (91.9%)	74/79 (93.7%)	61/69 (88.4%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	-1.8% (-11.3% , 7.7%)		
Azi - Comparator	3.5% (-7.7% , 14.7%)		

Azi/Metro - Comparator	5.3% (-5.4% , 15.9%)

MO Note: In the final visit LOCF population, 2 patients in the comparator group were already identified by the sponsor as failures. Seven patients were reclassified in the 15 Day post-therapy ITT population and 5 patients were reclassified in the final visit LOCF population.

Stat Note: Based upon DAIDP's Points to Consider, azithromycin alone could be considered therapeutically inferior to the azithromycin/metronidazole combination in the LOCF analysis because the lower bound of the 95% confidence interval is lower than -10%.

Summary of MO Bacteriological and Clinical Response for the Pathogens listed in the January 13, 1997 Proposed Package Insert.

Day 15 ITT Analysis

Pathogen	Azithromycin				Azithromycin/Metro				Comparative			
	Bact response		Clinical Response		Bact response		Clinical Response		Bact response		Clinical Response	
	E	P	C	F	E	P	C	F	E	P	C	F
Chlamydia trachomatis	14	0	14	0	20	0	20	0	24	0	24	0
N. gonorrhoeae	4	0	4	0	5	0	5	0	4	0	4	0
Mycoplasma hominis	8	2	8	2	12	3	12	3	7	2	7	2

E = Eradicated
P = Persisted
C = Cured
F = Failure

Subgroup analysis of efficacy in patients treated for PID under protocol #341 using the medical officer's evaluable patients group and the LOCF

Subgroup	n cured / N evaluable	% cured	n cured / N evaluable	% cured	n cured / N evaluable	% cured	p-value CMH
	azithromycin		azithromycin/metro		comparator		
< 45	66 / 72	92%	73 / 78	94%	58 / 66	88%	0.233
45-65	2 / 2	100%	1 / 1	100%	3 / 3	100%	
Days on IV [1]							
1 day	61 / 67	91%	60 / 65	92%	51 / 57	89%	0.249
2 days	7 / 7	100%	14 / 14	100%	9 / 11	82%	

[1] data missing for one patient

Stat note: No race analysis was performed because race was not provided in the SAS datasets. The study sites were located in Finland, Germany, Norway, Sweden, and the United Kingdom.

Safety

Summary of Adverse Events by body system -- All treated patients

	Number of Patients (1) with an adverse event (% of safety evaluable)		
	Azithromycin	Azithromycin/ Metronidazole	Comparator (2)
Number of Patients			
Evaluable for safety	76 (100.0%)	80(100.0%)	72 (100.0%)
With adverse event	19 (25.0%)	24 (30.0%)	25 (34.7%)
Discontinued due to adverse event	2 (2.6%)	3 (3.8%)	6 (8.3%)
Adverse Events by Body Systems			
musculoskelatal	0	1	0
skin and appendages	3	3	4
central & peripheral nervous system	2 (2.6%)	5 (6.3%)	3 (4.1%)
dizziness	2 (2.6%)	4 (5%)	2 (2.8%)
autonomic nervous	1	1	0
psychiatric	2	1	2
gastrointestinal	14 (18.4%)	13 (16.3%)	18 (11.1%)
diarrhea	5 (6.6%)	6 (7.5%)	2 (2.8%)
nausea	8 (10.5%)	7 (8.8%)	13 (18%)
abdominal pain	2 (2.6%)	2 (2.5%)	1 (1.4%)
vomiting	1 (1.3%)	3 (3.8%)	6 (8.3%)
appl./inj./incision/insertion site	1	3	0
special senses	0	1	1
cardiovascular	0	1	1
reproductive	1	2	0
vaginitis	1 (1.3%)	1 (1.3%)	0
general	0	4	5

(1) Patients counted once within each body system for multiple adverse events within the same body system.
(2) Comparative regimen consists of Metronidazole, Doxycycline, Cefoxitin and Probenecid.

Trial#2: Protocol 066-342:

A MULTICENTRE OPEN COMPARATIVE 3-WAY RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF IV AND ORAL AZITHROMYCIN IN COMPARISON WITH CO-AMOXICLAV AND DOXYCYCLINE IN THE TREATMENT OF PATIENTS WITH ACUTE PELVIC INFLAMMATORY DISEASE

Study Dates: July 29, 1991 - June 1, 1993

Countries participating in the study: Belgium (Center 109) , France (Centers 217, 218, 219, 460) , Italy (Centers 220, 221, 231, 232, 233) , Spain (Centers 209, 212, 226, 286).

Methods

Study Objective

To compare the efficacy and safety of azithromycin and azithromycin with metronidazole against co-amoxiclav (amoxicillin/clavulanic acid) and doxycycline (Vibramycin) in the treatment of acute pelvic inflammatory disease.

Study Methodology

Study Design

This was an open, multicenter, randomized, comparative study with clinical assessments to be made before treatment, on the second day of treatment, between the 7th and 9th days of treatment, at the end of treatment and at a follow-up assessment 39 to 44 days after the start of treatment. Bacteriological assessments were to be made before treatment, at the end of treatment and at the follow-up visit.

MO Note: Doxycycline was given as 100 mg orally b.i.d. for 21 days. Co-amoxiclav (Augmentin) was also given for a total of 21 days; 1 gm iv q8h for 5 days followed by 500 mg orally for 16 days. In the U.S., ampicillin/sulbactam is indicated for the treatment of gynecological infections.

Study Drug Administration

Duration:

Azithromycin alone was to be given as a 500mg dose iv once daily for 2 days, then 250 mg oral once daily for 5 days.

Azithromycin as in group 1 with concomitant metronidazole, either 500 mg iv q8h for the first 2 days followed by 500mg oral q8h for 10 days or 500mg oral t.i.d. for 12 days.

Doxycycline 100 mg oral b.i.d. for 21 days with concomitant amoxicillin and clavulanic acid 1g iv q8h for 5 days followed by 500 mg oral q8h for 16 days.

Analyses by the sponsor were performed identically to the those described for 066-341 so their descriptions will not be reiterated here.

Patients were to be hospitalized for a minimum of 24 hours or until the investigator regarded them as

suitable for ambulant therapy, whichever was the longer time. Clinical assessments were to be made before treatment, on the second day of treatment, between the 7th and 9th day of treatment, at the end of treatment and at a follow-up assessment 39-44 days after start of treatment. Bacteriological assessments were to be made before treatment, at the end of treatment and at the follow-up visit. Endometrial sampling was to be performed before treatment and at follow-up.

Inclusion, exclusion criteria, laboratory measurements and safety reporting were identical to what was described for protocol 341. Clinical observation was also similar with the following exception: Bacteriologic assessments were to be made post-treatment (13 to 18 days after start if treatment for azithromycin regimens 1 and 2, 20 to 23 days after start of treatment for doxycycline/co-amoxiclav regimen) and at follow-up. Endometrial sampling was to be performed at the follow-up visit only.

Sponsor's Efficacy Results

Patient Disposition:

Patients	Azithromycin	Azithromycin/ Metronidazole	Doxycycline/ Co-amoxiclav
Randomized to treatment	30	28	24
Received treatment	30	27	24
Discontinued treatment	0	3	1
Completed treatment	30	24	23
Clinical evaluation (ITT)	29	26	24
Bacteriological Response (ITT)	20	14	13

Reasons for Exclusion From Clinical Intent to Treat Analysis at End of Treatment:

Reason for Exclusion	Treatment Group	
	Azithromycin	Azithromycin/Metronidazole
Concomitant Antibacterial Therapy	1	0
Missing Data	0	1
Total Unevaluable	1	1

Reason for Exclusion from Bacteriological Intent to Treat Analysis at End of Treatment:

Reason for Exclusion	Treatment Group		
	Azithromycin	Azithromycin/ Metronidazole	Doxycycline/ Co-Amoxiclav
No Baseline Pathogen	9	11	9
Concomitant Antibacterial Therapy	1	0	0
Missing Data	0	2	2
Total Unevaluable	10	13	11

Number of Patients Enrolled by Center:

	Azithromycin		Azithromycin/ Metronidazole		Doxycycline/ Co-Amoxiclav	
Center	Randomized	Received Treatment	Randomized	Received Treatment	Randomized	Received Treatment
109	7	7	5	5	4	4
209	0	0	1	1	1	1
212	2	2	0	0	0	0
217	2	2	1	1	1	1
218	0	0	2	2	1	1
219	2	2	4	4	4	4
220	0	0	2	2	1	1
221	5	5	5	5	4	4
226	5	5	3	3	4	4
231	1	1	0	0	1	1
232	4	4	4	3	2	2
233	1	1	0	0	0	0
286	1	1	0	0	0	0
460	0	0	1	1	1	1
Total	30	30	28	27	24	24

Sponsor Results: (Patients included those with and without bacteriological assessments at end of therapy). Clinical success rate is based on the combination of cured + improved.

MO Note: Forty-one of the 79 end of treatment ITT population had a baseline laparoscopy. Fourteen, 12, and 15 patients had laparoscopy within each treatment arm above.

Cure rates by treatment and 95% confidence intervals of the difference in treatment cure rates for the medical officer's evaluable populations using ITT population at 15 day post-therapy visit and LOCF analysis for long term follow-up visit.

	Azithromycin	Azithromycin/ Metronidazole	Comparator
Day 15 ITT			
Cured	17/29 (58.6%)	12/26 (46.2%)	13/24 (54.2%)
Improved	12/29 (41.4%)	14/26 (53.8%)	9/24 (37.5%)
Clinical Success (cured or improved)	29/29 (100%)	26/26 (100%)	22/24 (91.7%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	0% (NA)		
Azi - Comparator	8.3% (-6.5% , 23.2%)		
Azi/Metro - Comparator	8.3% (-6.7% , 23.4%)		
At Long Term Follow-up Visit (Last Observation Carried Forward)			
Cured	22/29 (75.9%)	17/26 (65.4%)	15/24 (62.5%)
Improved	5/29 (17.2%)	4/26 (15.4%)	5/24 (20.8%)
Clinical Success (cured or improved)	27/29 (93.1%)	21/26 (80.8%)	20/24 (83.3%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	12.3% (-9.0% , 33.7%)		
Azi - Comparator	9.8% (-11.6% , 31.1%)		
Azi/Metro - Comparator	-2.6% (-27.8% , 22.7%)		

Stat Note: The Azi - Azi/Metro 95% CI was shown as NA because both treatments had 100% cure rates. Because of the very small sample sizes and the very high cure rates, the 95% confidence intervals that were provided are very wide.

Summary of Sponsor's Bacteriological and Clinical Response for the Pathogens in the January 13, 1997 Proposed Package Insert.

Day 15 ITT Analysis

Pathogen	Azithromycin				Azithromycin/Metro				Comparative			
	Bact response		Clinical Response		Bact response		Clinical Response		Bact response		Clinical Response	
	E	P	C	F	E	P	C	F	E	P	C	F
Chlamydia trachomatis	10	0	10	0	4	1	4	1	6	0	6	0
N. gonorrhoeae	2	0	2	0	0	0	0	0	1	0	1	0
Mycoplasma hominis	2	0	2	0	3	0	3	0	2	0	2	0

E = Eradicated
P = Persisted
C = Cure
F = Failure

Medical Officer's Efficacy Results

MO Comment: Review of the sponsor's data revealed one patient had persistent infection with Chlamydia trachomatis at the end of therapy. As discussed in the MO comment at the end of the previous study, this patient is considered a clinical failure as well. The patient was in the azithromycin/metronidazole arm.

MO Results: (Patients included those with and without bacteriological assessments at end of therapy).

Cure rates by treatment and 95% confidence intervals of the difference in treatment cure rates for the medical officer's evaluable populations using both ITT and LOCF analysis.

	Azithromycin	Azithromycin/ Metronidazole	Comparator*
Day 15 ITT			
Cured	17/29 (58.6%)	11/26 (42.3%)	13/24 (54.2%)
Improved	12/29 (41.4%)	14/26 (53.8%)	9/24 (37.5%)
Clinical Success (cured or improved)	29/29 (100%)	25/26 (96.2%)	22/24 (91.7%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	3.8% (-7.2% , 14.9%)		
Azi - Comparator	8.3% (-6.5% , 23.2%)		
Azi/Metro - Comparator	4.5% (-12.8% , 21.8%)		
At Long Term Follow-up Visit (Last Observation Carried Forward)			
Cured	22/29 (75.9%)	16/26 (61.5%)	15/24 (62.5%)
Improved	5/29 (17.2%)	4/26 (15.4%)	5/24 (20.8%)
Clinical Success (cured or improved)	27/29 (93.1%)	20/26 (76.9%)	20/24 (83.3%)
Difference in % clinical success (i.e. cured or improved) (95% CI)			
Azi - Azi/Metro	16.2% (-6.1% , 38.5%)		
Azi - Comparator	9.8% (-11.6% , 31.1%)		
Azi/Metro - Comparator	-6.4% (-32.4% , 19.6%)		

Stat Note: Because of the very small sample sizes and the very high cure rates, the 95% confidence intervals are very wide.

Summary of MO's Bacteriological and Clinical Response for the Pathogens in the January 13, 1997 Proposed Package Insert.

Day 15 ITT Analysis

Pathogen	Azithromycin				Azithromycin/Metro				Comparative			
	Bact response		Clinical Response		Bact response		Clinical Response		Bact response		Clinical Response	
	E	P	C	F	E	P	C	F	E	P	C	F
Chlamydia trachomatis	10	0	10	0	4	1	4	1	6	0	6	0
N. Gonorrhoae	2	0	2	0	0	0	0	0	1	0	1	0
Mycoplasma hominis	2	0	2	0	3	0	3	0	2	0	2	0

E = Eradicated
P = Persisted
C = Cure
F = Failure

Subgroup analysis of efficacy in patients treated for PID under protocol #342 using the medical officer's evaluable patients group and the LOCF

Subgroup	n cured / N evaluable	% cured	n cured / N evaluable	% cured	n cured / N evaluable	% cured	p-value CMH
	azithromycin		azithromycin/metro		comparator		
< 45	26 / 28	93%	19 / 25	76%	18 / 21	86%	0.233
45-65	1 / 1	100%	1 / 1	100%	2 / 3	67%	
Days on IV							
1 day			1 / 1	100%			0.387
2 days	27 / 29	93%	17 / 23	74%	0 / 1	0%	
3 days			2 / 2	100%			
4 days					1 / 1	100%	
4 days					19 / 22	86%	

Stat note: No race analysis was performed because race was not provided in the SAS datasets. The study sites were located in Belgium, France, Italy, and Spain.

Safety

Summary of Adverse Events by body system -- All treated patients

	Number of Patients (1) with an adverse event (% of safety evaluable)		
	Azithromycin	Azithromycin/ Metronidazole	Comparator (2)
Number of Patients			
Evaluable for safety	30 (100%)	27(100%)	24 (100%)
With adverse event	10 (33%)	12 (44%)	14 (58%)
Discontinued due to adverse event	0	1 (4%)	0
Adverse Events by Body Systems			
skin and appendages	1	1	1
central & peripheral nervous system	0	3	0
dizziness	0	2 (7.4%)	0
autonomic nervous	1	0	0
psychiatric	1	1	0
gastrointestinal	6 (20%)	8 (29.6%)	9 (37.5%)
diarrhea	2 (6.7%)	1 (3.7%)	2 (8.3%)
nausea	1 (3.3%)	4 (14.8%)	4 (16.7%)
abdominal pain	0	3 (11.1%)	4 (16.7%)
vomiting	1 (3.3%)	0	0
respiratory	0	0	1
cardiovascular	0	0	1
haemopoietic	1	0	0
reproductive	3	1	2
vaginitis	2 (6.7%)	1 (3.7%)	2 (8.3%)
general	1	2	2

(1) Patients counted once within each body system for multiple adverse events within the same body system.
(2) Comparative regimen consists of Metronidazole, Doxycycline, Cefoxitin and Probenecid.

Summary of Bacteriological Efficacy from Non-U.S. PID Trials:

Summary of Sponsor's Bacteriological Response for Studies 341 and 342 combined at the Day 15 ITT population for the Pathogens listed in the January 13, 1997 Proposed Package Insert.

	Azithromycin			Azithromycin/Metronidazole		
Pathogen	Total	Eradicated	Persistant	Total	Eradicated	Persistant
Chlamydia trachomatis	24	24 (100%)	0	25	24 (96%)	1
N. gonorrhoeae	6	6 (100%)	0	5	5 (100%)	0
Mycoplasma hominis	10	8 (80%)	2 (20%)	18	15 (83%)	3 (17%)

Safety Data from Non-U.S. PID Trials:

Safety data were available for 309 patients; 106 patients received azithromycin, 107 patients received azithromycin with metronidazole and 96 patients received an active comparator.

Comparative IV therapy in study 341 consisted of cefoxitin and metronidazole. Comparative oral therapy consisted of doxycycline, metronidazole, and probenecid. Comparative IV therapy in study 342 consisted of co-amoxiclav and comparative oral therapy consisted of amoxicillin-clavulonate and doxycycline.

Demographic Characteristics for 309 female patients in phase 3 PID studies:

Demographic Characteristic	Azithromycin	Azithromycin/ Metronidazole	Comparative Agent
Total # Patients	106	107	96
Age Groups 16-44 45-64	 101 5	 105 2	 90 6
Age (Years) Mean (SD) Range	60.6 (11.1)	62.1 (13.4)	60.9 (11.1)
Weight (kg) Mean (SD) Range	60.6 (11.1)	62.1 (13.4)	60.9 (11.1)
Race (%) White Black Asian Other	 97 (91.5) 6 (5.7) 1 (0.9) 2 (1.9)	 96 (89.7) 9 (8.4) 1 (0.9) 1 (0.9)	 86 (89.6) 10 (10.4) 0 0

Number of Dosing Days for IV Therapy--All Treated Patients for Studies 341 and 342

Number of Patients (%)			
Days IV Dosing	Azithromycin	Azithromycin/ Metronidazole	Comparative
2	73 (68.9)	79 (73.8)	70 (73.7)
3	33 (31.1)	28 (26.2)	2 (2.1)
5	0	0	1 (1.1)
6	0	0	22 (23.1)
Total Treated	106	107	95*

*One patient from the comparative group in study 341 received intramuscular cefoxitin for two days. This patient is excluded from this table.

MO Note: The Dosage and Administration section of the proposed package insert states that patients with PID should be treated with intravenous azithromycin for one or two days before being switched to oral therapy at the discretion of the physician. Roughly one-third of the patients in the azithromycin alone arm and one-quarter of the patients in the azithromycin/metronidazole arm received three days of intravenous therapy. The label should state patients should be treated for one to three days with intravenous azithromycin.

Summary of Adverse Events--All Treated Patients for Studies 341 and 342

Number of Patients (% of total treated)			
	Azithromycin	Azithromycin/ Metronidazole	Comparative
Patients Treated	106	107	96
Total # of Adverse Experiences	42	65	60
Patients with adverse events	29 (27.4)*	36 (33.6)	39 (40.6)
Patients with severe adverse events	2 (1.9)	5 (4.7)	5 (5.2)
Patients discontinued due to adverse events	2 (1.9)	4(3.7)	6 (6.3)
Patients with dose reduced/ temporarily suspended	1 (0.9)	2 (1.9)	2 (2.1)

*Number of Patients with at least one adverse event

Adverse events reported from studies 341 and 342

Events reported at >5% incidence

Treatment Group	Adverse Event	%
Azithromycin	Diarrhea	8.5
	Nausea	8.5
Azithromycin/Metronidazole	Diarrhea	7.5
	Nausea	10.3
	Dizziness	5.6
Comparative	Nausea	17.7
	Abdominal Pain	5.2
	Vomitting	6.3

Events reported at 1-5% incidence

Treatment Group	Adverse Event	%
Azithromycin	Anorexia	1.9
	Vomitting	1.9
	Dizziness	1.9
	Pruritus	1.9
	Rash	1.9
	Vaginitis	2.8
Azithromycin/Metronidazole	Stomatitis	1.9
	Dyspnea	1.9
	Injection site reaction	1.9
	Pruritus	1.9
	Vaginitis	1.9
Comparative	Stomatitis	1.0
	Glossitis	1.0
	Anxiety	1.0
	Dizziness	2.1
	Parasthenia	1.0
	Somnolence	1.0
	Pharyngitis	1.0
	Pruritus	3.1
	Rash	2.1
	Taste Perversion	1.0
	Vaginal Moniliasis	2.1
	Vaginitis	2.1
	Vulvovaginal disorder	1.0

MO Note: A review of laboratory data including hematocrit/hemoglobin, liver-associated enzymes, and electrolytes revealed no clinically meaningful changes. No discontinuations due to laboratory abnormalities were noted. This was noted in all arms of both studies.

No deaths were reported from either PID study.

VIII. Summary and Conclusions

The sponsor has submitted evidence to support the use of the intravenous formulation of azithromycin for the indications of community-acquired pneumonia and pelvic inflammatory disease.

For Community Acquired Pneumonia, intravenous Zithromax® should be indicated for patients who require initial intravenous therapy directed against the pathogens *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarhalis, Mycoplasma pneumoniae, Staphylococcus aureus* or *Streptococcus pneumoniae.* The duration of intravenous therapy should be two to five days depending on clinical response. This conclusion is based on two pivotal U.S. clinical studies submitted by the sponsor. Study 0618 demonstrated a cure + improvement rate of 77.7% for azithromycin versus a success (cure + improvement) rate of 73.9% for the comparator. The 95% confidence interval was -7%, 14.6%, thereby establishing therapeutic equivalence. These numbers are based on the medical officer evaluation. Neither gender nor age had an effect on the observed efficacy. Study 0625 was non-comparative and showed a success (cure + improvement) rate of 88.1%, also based on the medical officer evaluation. Eradication rates support the inclusion of the following organisms: *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella cararrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, and Streptococcus pneumoniae.*

For pelvic inflammatory disease, intravenous Zithromax® should be indicated for patients who require initial intravenous therapy directed against the pathogens *Neisseria gonorrhoeae, Chlamydia trachomatis, and Mycoplasma hominis.* The duration of intravenous therapy should be one to three days. This conclusion is based on two foreign studies submitted by the sponsor that were composed of women primarily under the age of 45.

Labeling Comment

In the INDICATIONS AND USAGE section, the following statement should be added,

The addition of this statement is suggested because of azithromycin's lack of anaerobic coverage and the following recommendations for treatment of PID by the Center for Disease Control and Prevention.

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HFD-520/MO/L. Girardi
HFD-725/BioStat/S. Bell
HFD-520/ProjMgr/J. Cintron
HFD-344/DSI/M. Thomas
HFD-725 Chron file
This review contains 83 pages and Attachment A: Listing of Deaths.

ATTACHMENT A

APPENDIX I U.S. and NON-U.S. PATIENT DEATH NARRATIVES

U.S. Phase III Studies

Deaths:

Patient No.	Treatment Group
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin

(Azithromycin)
discontinued due to serious adverse event - worsening pneumonia
death

Patient a 53-year-old White male, diagnosed with community-acquired pneumonia, was admitted and began treatment on 7/21/94. The patient had a current medical history significant for chronic obstructive pulmonary disease, pneumonia (four previous episodes) and emphysema. In addition, a CT scan of his chest (3/94) showed evidence of a pleural-based mass. He also had malnutrition and a history of smoking. A baseline chest X-ray revealed peripheral infiltrates in the right upper lung consistent with pneumonia. Clinical signs and symptoms at baseline included rhonchi, wheezes, consolidation, severe chest pain, moderate dyspnea, and a moderate cough. Physical examination also revealed decreased breath sounds. The patient's temperature at baseline was 97.9° F. Sputum and blood cultures were negative at baseline. The patient received one azithromycin 500 mg dose IV daily

from 7/21/94 through 7/24/94 (cumulative dose 2000 mg IV). Concomitant medications included Tylenol with codeine No. 3 (2 tablets on 7/22/94 and 4 tablets on 7/23/94) and acetaminophen (650 mg on 7/24/94 and 1300 mg on 7/25/94), all for chest pain. The patient also received triamcinolone, metaproterenol and ipratropium in the dosage of 16 puffs a day each for chronic pulmonary obstruction until 7/27/94. The patient was discontinued from the study drug treatment on 7/24/94, because his condition was not improving satisfactorily. On 7/23/94 the patient experienced increased shortness of breath, as well as nausea and vomiting on 7/27/94. The patient was found to have bilateral pleural effusions, but no cancer was diagnosed. He was intubated on 7/29/94 and on 8/5/94 the patient's family wished him to be extubated. He was pronounced dead on that same day.

(Azithromycin)

discontinued due to serious adverse events - congestive heart failure, acute hepatic and renal insufficiency, sepsis
death

Patient an 85-year-old White male, was admitted with a diagnosis of community acquired pneumonia and began treatment on 1/23/95. The patient had a current medical history of arrhythmias, atherosclerotic coronary artery disease, adult onset diabetes mellitus, and asthma. A baseline chest X-ray revealed marked left single lobe density suggesting infiltrate/atelectasis. Clinical signs and symptoms at baseline included rales, wheezes, moderate dyspnea, rare cough, and mucoid sputum. Also noted was mild throat erythema. The patient's temperature was 99.2° F. Sputum, blood and urine cultures were negative at baseline. Baseline liver function test laboratory findings included total bilirubin 0.7 mg/dL, SGOT (AST) 26 IU/L, SGPT (ALT) 11 IU/L, LDH 163 IU/L, and alkaline phosphatase 79 IU/L. The patient received azithromycin 500 mg IV daily for eight days (cumulative dose 4000 mg IV). On 1/31/95, the patient experienced severe congestive heart failure (CHF), sepsis, acute hepatic insufficiency, and acute renal insufficiency, all of which were considered by the investigator to be serious, and not related to study drug. Liver function tests obtained on this day included total bilirubin 1.4 mg/dL, SGOT (AST) 1563 IU/L, SGPT (ALT) 1110 IU/L, LDH 1704 IU/L, and alkaline phosphatase 135 IU/L. The patient also experienced the adverse events of moderate insomnia (1/23/95), nausea (1/23/95), constipation (1/27/95), trauma to rib cage from a hospital fall (1/27/95), anxiety (1/31/95), mild disorientation (1/28/95), and rib pain (1/29/95), none of which were considered to be related to study drug. The patient experienced mild IV infiltration on 1/25/95 that was considered to be due to study drug. On 1/31/95, the patient was transferred to the intensive care unit for acute respiratory distress, and subsequently died on 2/5/95 of CHF with probable sepsis from pneumonia, acute hepatic insufficiency, and prerenal azotemia, none of which were thought to be related to study drug.

(Azithromycin)
serious adverse event - acute respiratory failure
death

Patient a 66-year-old White male, was admitted with a diagnosis of community-acquired pneumonia and began treatment on 3/31/94. The patient had a current medical history of chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema, and was a former smoker. A baseline chest X-ray revealed moderate multilobar dense infiltrate of the left upper lobe and hyperexpanded lung fields consistent with pneumonia. Clinical signs and symptoms at baseline included abnormal respiratory rate, fever, rhonchi, consolidation, rigors, severe dyspnea, moderate coughing most of the time, and purulent sputum. Also noted were decreased breath sounds, a cyanotic ill appearance, and rales on the left side. The patient's temperature was 36.5 °C. His oxygen saturation obtained by pulse oximetry was 90% while receiving 32% O_2 by nasal cannula. Sputum, blood and urine cultures were negative at baseline. A urine antigen test for Legionella was negative. The patient received azithromycin 500 mg IV daily for three days, and 500 mg PO daily for seven days (cumulative dose 1500 mg IV and 3500 mg PO). On 4/4/94, the patient experienced mild bilateral pleural effusion that was considered to be caused by illness-precipitated congestive heart failure, and which was resolved by 4/14/94. The patient completed study therapy on 4/9/94, but experienced severe acute respiratory failure requiring rehospitalization and endotrachial intubation on 4/14/94. The patient was withdrawn from the study during the posttherapy phase and deemed a treatment failure. This adverse event was considered to be serious and the patient was treated with gentamicin, ceftazadime, timentin, and erythromycin for presumed pneumonia, and with methylprednisolone for wheezing. Small cell cancer of the lung was verified by a transthoracic needle biopsy on 4/21/94 and a CAT scan revealed metastatic disease in the liver. Concomitant medications administered during study drug therapy included methylprednisolone (400 mg IV and 120 mg IV), prednisone (60 mg PO and 40 mg PO), albuterol (32 puffs/daily), ipratropium (32 puffs/daily), and Robitussin® (30 mL PO). The patient died on 5/25/94.

(Azithromycin)
serious adverse event - respiratory failure
death

Patient a 59-year-old White male, was admitted with a diagnosis of community acquired pneumonia and began treatment on 10/18/94. The patient had a medical history of deep vein thrombosis, arthritis, sacral ulcer, and weight loss with decreased appetite. The patient had a past history significant for bronchitis and pneumonia, and was a former smoker. A baseline chest X-ray revealed marked right lung pleural fluid, and presence of underlying consolidation/atelectasis in right lung field was not excluded. Clinical signs and symptoms at baseline included rales, consolidation, rigors, moderate chest pain and dyspnea, and some moderate coughing. Also noted were a cachectic appearance, harsh crackles and decreased breath sounds over right lower lung, irregular heart rate and pulse, abnormal right axillary lymph nodes, and decreased vocal and tactile fremitis. The patient's temperature was 99.0°F. His oxygen saturation obtained by pulse oximetry on

10/21/94 was 71% while receiving 51% O_2 by nasal cannula. Sputum, blood and pleural fluid cultures were negative at baseline. The patient received azithromycin 500 mg IV daily for three days (cumulative dose 1500 mg IV). On 10/20/94 a bronchoscopy revealed right lung malignancy, and the patient was withdrawn from the study due to non-confirmation of infectious cause. The patient refused further work-up or treatment. On 10/21/94, the patient experienced severe respiratory failure, considered by the investigator to be a serious adverse event and due to his lung cancer. The patient requested that resuscitation be withheld, and respiratory failure progressed to arrest and death on the same day (10/21/94).

(Azithromycin)
serious adverse events - exacerbation of COPD, respiratory failure, persistent pneumonia
death

Patient a 77-year-old White male, was admitted with a diagnosis of community acquired pneumonia and began treatment on 12/26/94. The patient had a current medical history of atherosclerosis, cardiomegaly, mild anemia, severe chronic obstructive pulmonary disease, and emphysema. He had a past medical history significant for cancer of the larynx for which he had a laryngectomy, and he was a former smoker. A baseline chest X-ray revealed moderate left and right single lobe infiltrate representing pneumonia. Clinical signs and symptoms at baseline included abnormal respiratory rate, fever, rhonchi, wheezes, consolidation, severe dyspnea, some moderate coughing, and mucopurulent sputum. Tachycardia was also noted. The patient's temperature was 101.2° F. Blood, sputum and urine cultures were negative at baseline. The patient received azithromycin 500 mg/day IV for five days, and 500 mg/day PO for three days (cumulative dose 2500 mg IV and 1500 mg PO). Although the patient showed clinical improvement, a sputum culture obtained on 12/29/94 was positive for *Haemophilus influenzae*, indicating resistance (confirmed by reference laboratory result) to study drug, and the patient was discontinued due to insufficient clinical response on 1/2/95. The patient was treated with ceftazidime for pneumonia. The patient developed severe increased shortness of breath due to tracheostomal stenosis and underlying COPD on 1/2/95. On 1/3/95, the patient experienced severe respiratory difficulties necessitating transfer to ICU, considered by the investigator to be serious and not due to study drug. This adverse event was resolved and he was sent back to the floor on 1/11/95 after stomatoplasty on 1/10/95. On 1/3/95, the patient also experienced severe atrial fibrillation and rapid ventricular response (resolved 1/8/95), edema (resolved 1/12/95), and moderate shoulder pain (resolved 1/8/95). For these adverse events, on 1/3/95 the patient received concomitant treatment with theophylline 600 mg PO, furosemide 30 mg PO, adenosine 18 mg IV, diltiazem 45 mg IV, digoxin .75 mg IV, and morphine HCl 2 mg IV. On 2/7/95, the patient went into respiratory failure, his condition deteriorated, and he died on 2/11/95.

(Azithromycin)
serious adverse events - lung cancer, cardio-respiratory arrest
death

4 Patient a 74-year-old White male, was admitted with a diagnosis of community acquired pneumonia and began treatment on 3/9/95. The patient had a current medical history of atrial fibrillation, chronic obstructive pulmonary disease, and was a smoker. He had a past medical history significant for angina. A baseline chest X-ray revealed moderate left upper lobe infiltrate. The lungs were also hyperaerated with associated exaggeration of the lung markings, and possible atelectasis in the right lower lobe. Clinical signs and symptoms at baseline included abnormal respiratory rate, rales, moderate chest pain and dyspnea, some severe coughing, and mucoid sputum. Also noted were tachypnea, a few crackles in the left lung base, an irregular heart rhythm, and decreased bilateral breath sounds. The patient's temperature was 99.6° F. A sputum culture was positive for *Candida albicans*, considered to be a colonizer only, and a blood culture was negative at baseline. The patient received azithromycin 500 mg/day IV for two days (cumulative dose 1000 mg IV). The patient was discontinued from the study due to insufficient clinical response and no radiological improvement on the second day of treatment, and treated with cefuroxime, albuterol, and erythromycin for pneumonia. On 3/16/95, the patient was diagnosed with severe lung cancer that had been present, but undiscovered, prior to the study. On 3/25/95, the patient experienced a cardio-respiratory arrest. The patient was not resuscitated by his own request, and died on 3/25/95.

(Azithromycin)
serious adverse events - respiratory depression, hypotension, atrial fibrillation/flutter, respiratory acidosis, atrial flutter, renal failure, pulmonary edema
discontinued due to serious adverse events - respiratory acidosis, pulmonary edema
death

Patient an 81-year-old White female, was admitted with a diagnosis of community acquired pneumonia and began treatment on 2/14/95. The patient had a current medical history of aortic stenosis, stress incontinence, pancytopenia, degenerative joint disease, iron deficiency, sinusitis, back/hip pain, headache, rhabdomyosis (trauma from fall), dehydration, malaise and weakness. She had a past medical history significant for congestive heart failure in 1994, stabilized with Lasix. A baseline chest X-ray revealed marked multilobar left middle and lower lung consolidation consistent with pneumonia. Clinical signs and symptoms at baseline included an abnormal respiratory rate, rhonchi, moderate dyspnea, some moderate coughing, and mucopurulent sputum. Also noted were coarse breath sounds and systolic ejection murmur. The patient's temperature was 98.1 °F. Her oxygen saturation obtained by pulse oximetry was 86% while breathing room air. A sputum culture was positive for *Streptococcus pneumoniae*, and blood and urine cultures were negative at baseline. Elevated baseline liver function test results included total bilirubin 2.8 mg/dL, SGOT (AST) 210 IU/L, SGPT (ALT) 47 IU/L, and LDH 502 IU/L. The patient received azithromycin 500 mg/day for three days (cumulative dose 1500 mg IV). The last dose of study drug was administered on 2/16/95. On 2/14/95 the patient was mechanically ventilated, an arterial catheter was inserted, and nasogastric

suction was started. The patient developed moderate respiratory depression, requiring intubation, and hypotension on 2/15/95, both considered by the investigator to be serious and due to the disease under study. On 2/16/95, the patient had moderate atrial fibrillation and flutter, both considered by the investigator to be serious and due to aortic stenosis. On 2/17/95, the patient developed severe respiratory acidosis, renal failure, and pulmonary edema, all considered to be serious adverse events by the investigator and secondary to sepsis. Elevated liver function test results obtained on this day included total bilirubin 2.4 mg/dL, SGOT (AST) 181 IU/L, SGPT (ALT) 45 IU/L, and LDH 1111 IU/L. The patient died on 2/17/95 and death was ascribed to renal failure, secondary to sepsis. Medications received by the patient during hospitalization included dextrose solution, potassium chloride, temazepam, Darvocet-N, bisacodyl, albuterol, ferrous gluconate, lorazepam, dopamine hydrochloride, filgrastim, norepinephrine, midazolam hydrochloride, ranitidine, digoxin, sodium bicarbonate, bumetonive, furosemide, leverterenol hitartrate, midazolam HCl, ranitidine hydrochloride, digoxin, potassium chloride, heparin, epinephrine, and calcium chloride.

(Cefuroxime)

discontinued due to serious adverse events - congestive heart failure, hypoxemia death

Patient a 76-year-old White male, was admitted on 6/29/94 with a diagnosis of community-acquired pneumonia, and began treatment on 6/30/94. The patient had a current history of congestive heart failure (CHF), coronary artery disease, hypertension, gastric esophageal reflux, gastritis, transient hyperglycemia, chronic renal insufficiency, anemia, Parkinson's disease, dementia, depression, left lung nodule, degenerative joint disease, multiple falls, premature ventricular contractions, and nausea. He had a past medical history significant for chronic sinusitis, myocardial infarction (three events), and pneumonia. A chest X-ray on 7/2/94 revealed worsening moderate left patchy infiltrate. Clinical signs and symptoms on 7/1/94 included wheezes, mild chest pain, moderate dyspnea, some moderate coughing, and purulent sputum. Also noted was the presence of lung crackles. The patient's temperature was 98.1°F. A baseline sputum culture was negative. However, a sputum culture on 7/2/94 was positive for *Enterobacter agglomerans* and *Torulopsis glabrata*. A blood and urine culture obtained on 7/3/94, and a urine culture obtained the following day, were negative. The patient received cefuroxime 2250 mg/day IV for four days (cumulative dose 9000 mg IV). Erythromycin 1000 mg IV for one day, 2000 mg IV for one day, and 1000 mg IV for one day (cumulative dose 4000 mg IV), was administered concomitantly starting on 7/2/94, due to slow clinical response from the patient. The patient also received the concomitant medications of metaproterenol MDI, ipratropium bromide MDI, triamcinolone MDI, and pseudoephedrine, for shortness of breath and cough. On 7/3/94, the patient experienced severe CHF, hypoxemia and respiratory distress considered by the investigator to be serious and not related to study drug. The patient was discontinued from the study and moved to the intensive care unit, where he continued to deteriorate and died of cardiac arrest on 7/12/94. The cardiac arrest and subsequent death were considered by the investigator to be serious and not related to study drug. During the study, the patient also experienced the adverse

events of mild lethargy, and mild to moderate confusion, which were considered by the investigator to be unrelated to study drug, and moderate left arm pain, which was considered to be related to study drug. Other concomitant medications received by the patient included diltiazem, isosorbide dinitrate, divalproex, carbidopa/levodopa, selegiline, sertraline, ranitidine, furosemide, heparin, promethazine HCl, Mylanta®, and Tylenol®.

(Cefuroxime)
serious adverse event - cardiogenic shock
death

Patient a 77-year-old White male, was admitted with a diagnosis of community-acquired pneumonia and began treatment on 2/7/94. The patient had a current history of coronary artery disease and depression. He had a past medical history significant for congestive heart failure (CHF), aspergilloma of the left upper lobe (adequately treated in previous 6 months), and was a former smoker. A baseline chest X-ray revealed moderate right lower lobe infiltrate consistent with pneumonia. Clinical signs and symptoms at baseline included an abnormal respiratory rate, rales, wheezes, mild chest pain, moderate dyspnea, and rare mild cough. Also noted were white exudate on the tonsils and a III/VI holosystolic murmur at the apex of the heart. The patient's temperature was 97.0° F. His oxygen saturation obtained by pulse oximetry was 92% while breathing room air. Sputum was not obtained, and blood and urine cultures were negative at baseline. The patient received cefuroxime 750 mg IV for one day, 1500 mg IV for one day and 500 mg PO on that same day, and 1000 mg/day PO for the next eight days (cumulative dose 2250 mg IV and 8500 mg PO). The patient also received erythromycin 2000 mg IV for one day, 2000 mg IV for one day and 2000 mg PO that same day, 2000 mg/day PO for four days, 1000 mg PO for one day, and 2000 mg/day PO for five days (cumulative dose 4000 mg IV and 20,000 mg PO) concomitantly with cefuroxime. The last dose of study medication was taken on 2/16/94 and the last dose of erythromycin was taken on 2/19/94. Other concomitant medications included enteric coated aspirin 325 mg PO for heart disease, Zoloft® 50 mg PO for depression, isosorbide dinitrate 60 mg PO for coronary artery disease, and furosemide 20 mg PO and captopril 37.5 mg PO for CHF prophylaxis. On 3/24/94, the patient experienced severe cardiogenic shock, confirmed by urgent cardiac catheterization, and death, considered by the investigator to be serious and due to his coronary artery disease.

(Cefuroxime)
serious adverse event - pseudomembranous colitis
death

Patient a 66-year-old White male, was admitted with a diagnosis of community acquired pneumonia and began treatment on 4/25/94. The patient had a current medical history of watery diarrhea for four days, chronic renal insufficiency, chronic pancreatitis, urinary tract infection, peripheral vascular disease, chronic obstructive pulmonary disease, emphysema, fungal infection, chronic venous statis ulcers, and was a smoker. A baseline chest X-ray revealed minimal left lower lobe infiltrate, and moderate right lobe pleural effusion consistent with pneumonia. Clinical

signs and symptoms at baseline included rhonchi, rare mild cough, and mucoid sputum. Also noted were diminutions of breath sounds, pitting edema in arms and legs, and bilateral cervical lymphadenopathy. The patient's temperature was 98.2° F. Sputum, blood and urine cultures were negative at baseline. The patient received cefuroxime 750 mg IV for one day, 2250 mg/day IV for two days, 1000 mg/day PO for five days, and 500 mg PO for one day (cumulative dose 5250 mg IV and 5500 mg PO). The patient received Kaopectate® 60 to 120 cc/day (5/23/94 to 5/25/94 and 5/27/94 to 5/31/94), pancreatin 6 to 18 tablets/day (5/6/94 to 5/7/94, and 5/9/94,– ongoing), loperamide 4 mg (5/5/94), and Imodium® 6 mg/day (5/7/94 to 5/8/94), concomitantly for diarrhea. On 5/23/94 the patient experienced moderate worsening diarrhea. A stool culture obtained on 5/25/94 was positive for *C. difficile* toxin. On 5/27/94, the patient experienced severe pseudomembranous colitis for which the patient was given vancomycin 750 mg/day PO (5/27/94 to 5/31/94). The investigator considered the colitis to be serious and due to liver disease complicated by sepsis, renal insufficiency, pneumonia, and hepatic encephalopathy. The patient was re-admitted to the hospital from the extended care center attached to the institution, and left the hospital after two weeks against medical advice. The patient died on 6/21/94. An autopsy was done. The death certificate listed liver disease complicated by sepsis, renal insufficiency, pneumonia, and hepatic encephalopathy as causes of death.

(Cefuroxime)
discontinued due to serious adverse event - cardiac arrest
death

Patient a 65-year-old White male, was admitted and began study drug treatment on 6/14/94 with a diagnosis of community acquired pneumonia. The patient had a current medical history that was significant for angina, arteriosclerotic cardiovascular disease, and hypertension. The patient's past medical history was significant for cancer of the larynx which led to a glossectomy and to the patient receiving a peg tube, both in 1992. His only history of allergies were to acetylsalicylic acid. A baseline chest X-ray revealed a moderate right lobar infection consistent with pneumonia, however, a cavitary tumor could not be ruled out as a possibility. Clinical signs and symptoms at baseline included rales, rhonchi, wheezes, consolidation, moderate dyspnea, moderate cough, and purulent sputum. The patient's temperature was 98.0° F. His oxygen saturation obtained by pulse oximetry was 88% while breathing room air. Sputum cultures taken at baseline were positive for *K. pneumoniae*. Blood cultures were negative at baseline. The patient received cefuroxime 2250 mg/day IV for seven days, from 6/15/94 through 6/21/94, then 1500 mg IV on 6/22/94 and 500 mg PO on that same day, 1000 mg PO the following day, and 500 mg PO on 6/24/94, the tenth day of his treatment (cumulative dose 17,750 mg IV and 2000 mg PO). On 6/23/94, the patient's WBC count was still elevated at 14.3 and his SGOT and SGPT were elevated at 174 IU/L (ascribed to dehydration by the investigator) and 50 IU/L, respectively. Chest X-ray revealed an overall improvement but continuing right upper lobe cavitary lesion. The patient ceased to breath on 6/24/94, the day of his last dose of study medication, due to cardiac arrest.

(Azithromycin)
discontinued due to condition consistent with anaerobic infection
serious adverse events - hemoptysis, hypoxia
death

Patient - 281, a 47-year-old Black male, was admitted with a diagnosis of community-acquired pneumonia on 5/7/94 and began treatment on 5/8/95. The patient had a past medical history of cerebral vascular accident (multiple) and a current condition of hypertension, pleuritic chest pain, constipation, hemorrhoids, urinary tract infection, anemia, seizure disorder, left hemiparesis, left leg pain and syncopal episodes. He also had had pneumonia when he was 18 years of age and had been an alcohol user prior to 1990. The patient still used tobacco. His baseline X-rays showed marked zone infiltration of the right lung. Clinical signs and symptoms at baseline indicated that the patient had an abnormal respiratory rate, fever, rales, rhonchi, consolidation, and a rare cough. The patient's temperature at baseline was 100.9 °F. His oxygen saturation was 95% with 50% oxygen from a mask as measured by pulse oximetry. Sputum cultures isolated at baseline were negative. The patient was noted to have hemoptysis on the day of admission to the hospital. The patient received only 500 mg IV azithromycin on 5/7/94. Concomitant medications included warfarin therapy (5 mg/day) and pentoxifylline (1200 mg/day) for prophylaxis of CVA and captopril (6.25 mg/day) for hypertension. A second review of the patient's baseline criteria on 5/8/94 indicated that his condition was most consistent with an anaerobic infection, and he was discontinued from study medication. The patient then developed hemoptysis and was transferred to the ICU. On 5/8/94 the PT was similar to baseline (24.7 to 27.3 seconds) but the PTT (not done at baseline) was 60.3 seconds. At this point, warfarin was stopped due to the onset of hemoptysis. On 5/14/94 the patient suffered severe hypoxia, secondary to prior aspiration of blood which was secondary to necrotizing pneumonia. Resuscitation was attempted, but the patient died that day. None of the adverse events leading to death were considered to be related to study drug.

(Azithromycin)
discontinued due to insufficient clinical response
serious adverse event - persistent pneumonia, sepsis
death

Patient an 86-year-old White male, was diagnosed with community-acquired pneumonia on 11/13/94 and admitted on the same day. The patient had a medical history of abdominal aortic aneurysm and atherosclerotic cerebrovascular disease, depression, degenerative joint disease, seborrheic dermatitis and neurogenic bladder. He also suffered from blindness and had had multiple pneumonia episodes in the past. His baseline chest X-ray revealed that his lungs were hyperinflated, his heart was at the upper limit of normal in size and there was evidence of extensive infiltrates of the lung bases, bilaterally. These infiltrates appeared to be affecting both the interstitial space and the pulmonary alveoli. Clinical signs and symptoms at baseline included rales and rhonchi, mild dyspnea and mild cough. The patient also had mucopurulent sputum. The patient's baseline temperature was 99.0 °F. Baseline sputum cultures revealed *S. pneumoniae*, susceptible to azithromycin, as a pathogen. The patient received 500 mg/day IV of azithromycin from 11/13/94 to 11/17/94. He then received 500 mg/day of azithromycin PO for the next three days (cumulative dose 2500 mg IV and 1500 mg PO). The patient seemed to be responding well to study medication; however, on 11/20/94 the patient's condition suddenly worsened and he was taken off study medication. The patient developed an increased cough, and chest X-rays showed that there was an increased infiltration in the right lower lobe. The patient's temperature rose to 101.2 °F, and his white blood cell count increased. The condition could have been the effect of a superinfection but no culture could be obtained. The patient was switched to Bactrim IV therapy on 11/21/94, which produced no improvement in the patient's condition. The patient died after receiving three doses of Bactrim.

(Azithromycin)
discontinued due to death
serious adverse event - cardiac arrest

Patient a 60 year old Black male, was diagnosed with community-acquired pneumonia on 2/10/95 and admitted the same day. He had a medical history which included congestive heart failure, cor pulmonale, hypertension, chronic renal insufficiency, and chronic obstructive pulmonary disease (COPD) which included bronchitis and emphysema. All of these conditions were present at baseline. Other presenting conditions included rectal prolapse, hypomagnesemia, chronic glomerulonephritis, icthyosis and sleep apnea. The patient was also a chronic alcohol and tobacco user. A sputum culture was negative at baseline. Baseline X-ray results showed that the patient's heart was enlarged and there was some pulmonary vascular prominence in the lung interstices at the bases, which was suspected to be due to COPD. Clinical signs and symptoms at baseline revealed an abnormal respiratory rate of 33 resp/min and decreased breath sounds with the presence of moderate to severe respiratory distress. The patient also had a fever, rales, rhonchi and rigors with mild dyspnea and a mild cough. He had mucopurulent sputum and a sputum

volume of 100 mL/24 hours. The patient's temperature at baseline was 39.8 °C. He had an oxygen saturation of 97% measured by pulse oximetry while receiving 48% oxygen by mask. The patient received azithromycin by IV 500 mg/day from 2/10/95 to 2/13/95. He then received 250 mg/day of azithromycin orally on 2/14/95 and 500 mg/day of azithromycin on 2/16/95 (cumulative 2000 mg IV and 750 mg orally). Concomitant medications included albuterol inhaler and theophylline 200 mg/day on 2/10/95-2/16/95, both for the treatment of chronic lung obstruction. The patient showed improvement with the use of the study medication but still required supplemental oxygen. On 2/16/95 the patient suffered a cardiac and respiratory arrest which were the results of chronic pulmonary disease and hypoxemia. The patient died on 2/16/95; no autopsy was performed.

(Azithromycin)
discontinued due to insufficient clinical response
serious adverse events - pulmonary edema, respiratory failure, malignant cells in pleural fluid, sepsis
death

Patient 244, an 85-year-old Hispanic female, was diagnosed with community-acquired pneumonia on 10/24/94. She had been admitted to the hospital the previous day. She had recently recovered from an episode of pneumonia (within the past 14 days) for which she had received cefuroxime. She also had a medical history of coronary artery disease, hypertension, stroke gastrointestinal bleed, malnutrition, non-insulin dependent diabetes, anemia, dementia, hypoxemia, left lower lobe pneumonia with effusion, left arm flaccidity, dehydration and glaucoma. Her baseline chest X-ray revealed moderate partial opacification of the left chest, which was due to a combination of pleural effusion and left lower lobe infiltration or atelectasis. A partial infiltration was also seen in the right lower lobe. Clinical signs and symptoms indicated that the patient had an abnormal respiratory rate, rhonchi, and mild dyspnea at baseline. The patient's baseline temperature was 98.0 °F. Her sputum volume was 10 mL/24 hours. Her oxygen saturation was 96% with 100% oxygen administered by a mask and measured by pulse oximetry. Baseline cultures showed two biotypes of *E. coli* as colonizers in the urine. Baseline blood cultures revealed the 24-hour growth of a micrococcus species which was macrolide-susceptible. Bronchial cultures indicated *K. pneumoniae* of borderline susceptibility and an azithromycin-susceptible *S. aureus*. The patient received azithromycin 500 mg/day IV for five days (cumulative dose 2500 mg IV). On 10/26/94 the patient was diagnosed with malignancy from examination of epithelial cells from the pleural fluid. On 10/28/94 the patient experienced hypoxemia which was considered by the investigator to be severe in intensity and due to sepsis and the pleural effusion. On 10/29/94, during the course of treatment the patient experienced respiratory failure which was considered by the investigator to be severe in intensity and related to the disease under study. She was discontinued from study drug for lack of clinical response and given ceftazidime (2g/day), clindamycin (300 mg/day) erythromycin IV (500 mg/day) and ceftriaxone IV (1 g/day) on 10/29/94 and erythromycin (1000 mg/day) on 10/30/94, all for the treatment of sepsis. The patient died on 10/30/94 with a concluding diagnosis of sepsis, dehydration and gastrointestinal bleeding.

(Azithromycin)
discontinued due to adverse event - extreme lethargy
death

Patient an 84-year-old White male, was admitted on 2/20/95 with a diagnosis of community-acquired pneumonia. The patient had a medical history of aortic aneurysm, hypertension, and multiple CVAs and a current condition of aortic stenosis, arteriosclerotic peripheral vascular disorder, congestive heart failure and coronary artery disease. The following conditions were also present at baseline, degenerative joint disease, gout, and Raynaud's syndrome. His baseline X-ray did not show an infiltrate but a later film of 2/23/95 showed a right lower lobe infiltrate and signs of congestive heart failure. Clinical signs and symptoms at baseline indicated that the patient had an abnormal respiratory rate, fever, rales, rhonchi, wheezes, consolidation, rigors, a mild case of dyspnea, and a severe cough most of the time. The patient's sputum was purulent at baseline and his sputum volume was 100 mL. The patient's baseline temperature was 38.8 °C. The patient's oxygen saturation measured by pulse oximetry was 80% with room air and 88% with 36% oxygen via a nasal cannula at baseline. Baseline sputum cultures were negative, but blood cultures revealed *S. pneumoniae* susceptible to azithromycin. The patient received azithromycin 500 mg/day IV on 2/20/95 to 2/23/95. He received no study medication on 2/24/95 due to a nursing error. He resumed treatment on 2/25/92 with 500 mg/day of azithromycin by IV for two days. On his final day of treatment, 2/27/95, he received 500 mg/day of azithromycin PO (cumulative dose 3000 mg IV and 500 mg PO). Concomitant medication included acetaminophen 1300 mg/day and 650 mg/day on 2/21/95 and 2/23/95, respectively for pain and albuterol (nebulizer) for pneumonia on 2/27/95 to 2/28/95. The patient became extremely lethargic on 2/27/95, at which time azithromycin was discontinued. He was noted to be much less lethargic on the next day, and the investigator considered the lethargy to be related to study drug. He was treated with other antibiotics (cefazolin IV) from 3/4/95 to 3/7/95 due to continuing signs of pneumonia. The patient was discharged to a nursing home on 3/7/95 and died on 3/11/95 of natural causes.

(Azithromycin)
serious adverse event - cardio-respiratory failure
death

Patient a 62-year-old White male, was diagnosed with community-acquired pneumonia on 6/24/94 and was admitted the same day. The patient had anemia and aspiration disorder as a result of a tracheoropharyngeal fistula repair from 1986. In addition, the patient had chronic bronchitis and chronic obstructive pulmonary disease upon entry. Due to these conditions the patient had received amoxicillin (750 mg/day) from 6/10/94 to 6/20/94 and erythromycin (1 g/day) from 6/9/94 to 6/19/94. Baseline chest X-rays indicated bilateral basilar infiltrates. A comparison of the baseline X-ray with chest X-rays obtained one year earlier indicated that the patient's heart was slightly enlarged and there was evidence of extensive chronic pleural and parenchymal disease, suggesting heart failure with chronic pulmonary disease. Clinical signs and symptoms revealed that the patient had an abnormal respiratory rate, of 40 resp/min at baseline, rales, rhonchi, wheezes,

consolidation, moderate dyspnea and moderate cough. The patient's baseline temperature was 98.0 °F. The patient's baseline oxygen saturation was 89% with room air and 99% with 28% oxygen from a nasal cannula. Sputum and blood cultures were negative at baseline. The patient received 500 mg of azithromycin on 6/24/89. The patient had low values of red blood cell count, hemoglobin and hematocrit due to his anemia, and elevated glucose, sodium and chloride due to stress and dehydration. The patient developed hypoxia after the first day of treatment. Attempts were made to intubate the patient; however, these attempts failed due to the patient's prior tracheal surgery. On 6/25/94 the patient suffered a cardiac and respiratory arrest due to the disease under study and could not be resuscitated.

(Azithromycin)
serious adverse events - angina, acute anterior myocardial infarction
death

Patient an 84-year-old White female, was diagnosed with pneumonia and admitted on 1/13/95. The patient had a medical history of coronary artery disease, hypertension, congestive heart failure, depression and malnutrition which were all present at baseline. She had recently suffered from sinusitis which was treated with antibiotic (unknown sulfa drug) just prior to enrolling in the study. Her past medical history was also significant for colon cancer (6 years ago), and multiple ischemic attacks. Her baseline chest X-ray showed the she had a lower left lobe infiltrate and that her heart was enlarged with cephalization of vasculature, bilateral pleural effusions, and Kerley B lines at the right base, all indicating the presence of heart failure. Clinical signs and symptoms at baseline included fever, rales, consolidation, and rigors. She had mild dyspnea and a moderate cough. Her baseline temperature was 38.7 °C. Her oxygen saturation measure by pulse oximetry was 98% while receiving 28% oxygen through a nasal cannula. Culture results showed no organism growth. The patient received 500 mg/day IV of azithromycin from 1/13/95 to 1/15/95. For the following four days she received 500 mg/day PO of azithromycin (cumulative dose 1500 mg IV and 2000 mg PO). Concomitant medications included furosemide (20 mg daily) on days 1/15/95 and 1/17/95 for edema, verapamil (120 mg/day) on 1/18/95 for hypertension, dipyridamole (75 mg/day) on 1/18/95 for angina and coronary disease, and nitroglycerin (topical paste) on 1/17/95 to 1/19/95 and morphine sulfate IV (6 mg/day) on 1/17/95 for chest pain. On 1/17/95 the patient suffered an acute myocardial infarction. The patient collapsed on 1/22/95 and no attempts were made to revive her per the patient's wishes. The investigator ascribed death to the patient's underlying coronary artery disease.

Non-U.S. Phase III Studies

Deaths:

Patient No.	Treatment Group
	Azithromycin
	Azithromycin
	Azithromycin

Patient No.	Treatment Group
	Azithromycin
	Comparator
	Comparator
	Azithromycin
	Azithromycin
	Azithromycin
	Cefuroxime
	Cefuroxime
	Cefuroxime
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin
	Azithromycin

This 67 year old female started study treatment on 21st February 1992, days after the onset of pneumonia. An X-ray taken the day before the start of treatment showed a moderate single lobar pneumonia and pulmonary oedema with right basal effusion. Blood and sputum cultures were negative. The patient suffered from rheumatoid arthritis and had received long-term therapy with prednisolone and naproxen. Other concomitant medication were ipratropium and salbutamol, which were started on the second day azithromycin treatment. After three days of treatment with intravenous azithromycin, clinical improvement indicated a switch to oral treatment. On 24th February 1992, the day when oral treatment was started, heart failure was clinically diagnosed and an X-ray showed worsening pulmonary oedema. The patient was treated with frusemide, but suffered a cardiac arrest the following day and was withdrawn from the study. She died two days later. The investigator considered that death was due to underlying heart disease and was not related to study drug.

This 51 year old male with a 10 year history of chronic spastic bronchitis was hospitalised for an acute respiratory illness that had been present for the previous two weeks. He had no history of allergies, asthma or eczema. Chest X-ray showed a marked single lobar pneumonia; blood and sputum cultures were later shown to be negative. Verapamil was given for tachycardia and aminophylline because of the patient's history of bronchitis and to ease his dyspnoea. Treatment with intravenous azithromycin was started approximately 38 hours after hospitalisation. The patient's dyspnoea increased about 6 hours after the start of treatment: this was diagnosed as bronchospastic attack and treated with hydrocortisone. Later the patient became agitated and was sedated with diazepam. His condition continued to deteriorate with severe dyspnoea and respiratory and

circulatory failure. Azithromycin was discontinued and replaced with metronidazole. Furosemide and lanatoside C were also started and hydrocortisone continued but the patient died about 29 hours after the start of study treatment. While dyspnoea was present up to the patient's death it remains uncertain whether it was due to the bronchospastic attack or the progressing pneumonia. An autopsy revealed pulmonary oedema, diffuse mucopurulent tracheobronchitis and bilateral confluent pneumonia with an abscess in the left upper lobe. The left ventricle was dilated and there was a moderate degree of central and peripheral atherosclerosis. The investigator's opinion is that the severe dyspnoea diagnosed as bronchospasm could have been aggravated by azithromycin (although he considers this unlikely). He also felt that it was not possible to determine a single cause of the dyspnoea because of the presence of other possibly contributory factors (fulminating pneumonia with abscess formation and pulmonary oedema). The investigator felt that the profound deterioration of the patient's condition was due to fulminating bilateral pneumonia with abscess formation and this, together with the resulting respiratory and circulatory failure was the cause of the patient's death. The sponsor's opinion is that azithromycin was not directly contributory to the patient's death.

This 57 year old male with a history of brain tumour (removed in 1991) started study treatment on 26th May 1992. He had been given bromhexine for his respiratory condition on the same day but this was stopped before he entered the study. The baseline X-ray showed a moderate single lobar pneumonia, blood culture was negative and there was insufficient sputum for culture. On the third day of treatment the patient had a sudden deterioration with respiratory and circulatory failure and azithromycin was discontinued. Penicillin, gentamicin and metronidazole were instituted, but the patient died on 31st May 1992. An autopsy showed bilateral confluent bronchopneumonia with effusion in both pleural cavities. It was also noted that the patient's glioma was spreading and he was cachexic. Death was due to respiratory and circulatory failure which the investigator considered was due to severe bilateral pneumonia.

This 42 year old male with a history of ischaemic heart disease entered the study on 10th July 1992 with an X-ray showing minimal lobar infiltrates and no bacteriological confirmation of disease. He received intravenous azithromycin for 3 days. Concomitant therapies were aminophylline, aspirin, bromhexine, isosorbide mononitrate and verapamil. He was withdrawn from the study on 13th July 1992 due to an acute myocardial infarction and died the following day. An autopsy confirmed a recent infarct of the posterior part of the left ventricle and the apex of the heart. The investigator judged that death was due to intercurrent illness and not related to study drug.

This 81 year old male started study treatment on 23rd August 1992, 2 days after the onset of pneumonia. Baseline X-ray showed a marked single lobar pneumonia, but sputum and blood cultures were negative. The patient had a history of non-insulin dependent diabetes mellitus, gastritis/oesophagitis and congestive cardiac failure. Concomitant therapies at study entry were paracetamol, gliclazide, heparin, metoclopramide and omeprazole. Enalapril was started on the second day of treatment and lactulose on the third. On the fourth day of study treatment (26th

August 1992) an X-ray showed pleural effusion but the patient had shown a slight clinical improvement and was switched to oral amoxycillin. Oral erythromycin was added the following day. Both treatments were stopped on Ist September 1992 due to no further improvement and cefuroxime was started. On the same day the investigator noted rapid deterioration due to congestive heart failure (frusemide had been started the day before). Amoxycillin/clavulanic acid therapy replaced cefuroxime on 4th September and a normal X-ray was noted 3 days later. The patient died of congestive cardiac failure on 18th September, 17 days after completing study treatment. The investigator considered that death was due to underlying disease and not related to study drug.

This 81 year old female with oesophageal stenosis, circulatory insufficiency and cachexia entered the study on 24th April 1992. An X-ray taken the previous day showed a marked diffuse or patchy pneumonia and S. *pneumoniae and H. influenzae* were cultured from a sputum sample. The patient was treated with intravenous penicillin G for 7 days and showed clinical improvement with negative culture. However, she was withdrawn from the study because of inability to swallow oral medication and intramuscular ampicillin was started. The patient died on 2nd May 1992, 2 days after discontinuing intravenous penicillin G. This investigator gave cause of death as cachexia and an autopsy showed a carcinomatous infiltration in the medial part of the oesophagus. The investigator considered that death was not related to study drug.

This 81 year old male had an acute onset of presumed bacterial pneumonia on 16th March 1992. He presented with a mild cough productive of mucopuruient sputum which occurred most of the time, severe dyspnoea, rales, rhonchi and crepitations. The X-ray showed bibasilar infiltrates with minimal effusions and *H.influenzae* was isolated from the sputum. No blood sample was collected. On admission the patient was already taking prednisolone, having oxygen delivered by a face mask and receiving intravenous bumetanide. The patient was given a single intravenous dose of azithromycin on 17th March 1992 and concomitant oral erythromycin. Salbutamol and ipratropium inhalers were also started. The patient began to feel slightly better on the 18th March before suffering a fatal cardiac arrest. The autopsy carried out the following day confirmed the patient had died of cardio-respiratory failure. There was severe diffuse emphysema and bronchitis throughout each lung with bilateral pulmonary oedema. There was no evidence of pulmonary embolus or pneumonia. The investigator considered that death was due to the underlying chronic obstructive airways disease and not related to study treatment.

This 83 year old male had an acute onset of presumed bacterial pneumonia on 9th April 1992. The patient presented with crepitations and dullness on percussion. X-ray report showed minimal patchy change at base of right lung and minimal effusion at base of left lung. Blood cultures were negative and no sputum was collected. He had a past history of non-insulin dependent diabetes, ischaemic heart disease and hypothyroidism for which he was receiving glibenclamide and thyroxine. His liver function tests were abnormal at baseline and the investigator considered this could be due to heart disease and anoxia but other abnormalities were to be excluded. The patient received azithromycin for 7 days - 2 days

intravenously and 5 days orally. The clinical signs and symptoms resolved gradually over 10 days although the patient's clinical condition was poor throughout the study and was therefore difficult to assess the progress of the pneumonia. The patient received aspirin, vitamin K, amiloride/frusemide, heparin and paracetamol concomitantly from 11th April; heparin was stopped on 14th April and paracetamol on 23rd April. On 22nd April the patient was diagnosed as having adenocarcinoma of the duodenum, biopsy also revealed liver metastases, from which he died on 9th May. The investigator considered death was due to the underlying carcinoma and was not related to study drug.

This 79 year old male entered the trial on 29th January 1992 with a presumptive clinical diagnosis of bacterial pneumonia, having received a single 500 mg intravenous dose of ampicillin in the 2 weeks prior to study start. The patient presented with an occasional moderate cough, moderate dyspnoea, crepitations and dullness on percussion. X-ray showed a marked single lobar pneumonia. Blood culture was negative and *S. aureus* was isolated from the sputum. Nebulized salbutamol was started on 29th January. Underlying diseases of gout and chronic obstructive airways disease were also present and on entry into the study the patient was taking allopurinol, indomethacin and frusemide. At 72 hours blood culture was again negative and *S. pneumoniae* was found in the sputum. The clinical signs and symptoms did not resolve and the patient was withdrawn from the trial on 6th February having received azithromycin for 5 days intravenously and 5 days orally and completed treatment. The patient suffered acute left ventricular failure on 4th February for which a single intravenous infusion of isosorbide dinitrate was administered; amiloride/frusemide was also given at this time. Lung cancer was diagnosed on 6th February and erythromycin and prednisolone were started on 7th February. The patient died of lung cancer on 10th February 1992. The investigator considered that death was due to the underlying cancer and not related to study drug.

. This 78 year old female suffered an acute onset of presumed bacterial pneumonia on 21st December 1991. She presented with a moderate cough which occurred most of the time, rales, crepitations and dullness on percussion. X-ray showed a marked bibasilar or bilateral lobar infiltrate. Blood culture was negative and no sputum was collected. The patient was treated with intravenous cefuroxime, of variable doses, from 22nd December and also given nebulized salbutamol and oxygen via a face mask to improve breathing. The cough improved gradually over the following 6 days and there was mild dyspnoea for 2 days. The patient suffered an acute myocardial infarction, acute pulmonary oedema and cardiogenic shock on 24th December for which dopamine, dobutamine and heparin were given; frusemide was added on 26th December. An X-ray taken on 24th December showed continued infection together with left ventricular failure. This patient was also treated with intravenous erythromycin from 24th to 29th December. She died at 1AM on 29th December 1991 of an acute coronary thrombosis. The investigator considered that death was not related to study drug.

This 82 year old female was admitted to hospital on 11th March 1992 with a presumptive clinical diagnosis of bacterial pneumonia. The patient presented with severe dyspnoea and a cough together with rhonchi and crepitations. Her X-ray

showed a moderate single lobar opacity, blood culture was negative and no sputum was collected. The patient suffered from congestive heart failure for which she was receiving digoxin, frusemide and acetazolamide. She had also recently had a cataract operation for which indomethacin, sodium chloride and Decadron/Neomycin eye drops were administered. The patient received two intravenous doses of 750 mg cefuroxime. Her condition deteriorated suddenly overnight and at first the physician diagnosed a myocardial infarction. She died later that night (11th March). The autopsy carried out the following day revealed a severe pulmonary thromboembolism and infarction of the right lower lobe as seen on X-ray. There were no clear signs of a myocardial infarct and no infection was found. The investigator considered that death was due to the underlying disease and was not due to study drug.

This 92 year old male received one intravenous dose of 750 mg cefuroxime on 12th November 1992 for a presumptive clinical diagnosis of bacterial pneumonia. The patient was confused and showed severe dyspnoea. The Xray taken on the day of treatment showed a marked bibasilar or bilateral lobar infiltrate. Blood culture was negative and no sputum was collected. The patient was treated concomitantly with intravenous heparin, aminophylline (for emphysema), dexamethasone (for pneumonia) and was also given oxygen. The patient died of his pneumonia about 12 hours after entering the trial. The investigator considered that death was due to pneumonia and was not related to study drug.

This 79 year old female started study treatment on 30th August 1993, 3 days after the onset of acute bronchitis. The patient had a history of ischaemic heart disease and chronic obstructive pulmonary disease and was receiving diltiazem, furosemide, heparin, hydrocortisone, isosorbide dinitrate and metolazone at study entry. A physical examination on the first day of treatment revealed mitral regurgitation and ankle oedema. The patient was treated with azithromycin for 7 days (2 intravenous, 5 oral) with improvement of the symptoms of infection and eradication of the baseline pathogen *(Moraxella catarrhalis)*. However, deteriorating cardiovascular status was indicated from 1st September 1993, when unstable angina was reported. Anaemia related to uraemia, gastrointestinal bleeding, epistaxis and haemoptysis was reported on 6th September and the investigator noted worsening heart failure on 7th September. The patient died of pulmonary oedema due to ischaemic heart disease on 19th September 1993, 14 days after completing treatment with azithromycin. The investigator considered that death was due to underlying heart disease and was not related to study drug.

This 68 year old male started study treatment on 3rd October 1993, the day after the initial diagnosis of acute exacerbation of chronic bronchitis. The patient had a 15 year history of congestive cardiac failure and atrial fibrillation and was also suffering from non-insulin-dependent diabetes mellitus. Long-term treatments with allopurinol, amiloride/hydrochlorothiazide, digoxin, ipratropium, potassium, ranitidine and salbutamol continued through the study period. Blood and sputum cultures at baseline (3rd October) revealed no pathogens, but the investigator recorded septicaemia. The patient was treated with intravenous azithromycin for 3 days, but was withdrawn due to lack of efficacy before dosing on 6th October. Blood and sputum cultures on 5th and 6th October respectively showed *Serratia*

marcescens, an organism known to be resistant to azithromycin. The patient suffered a cardiac arrest later the same day and was transferred to the intensive care unit where he died the following day (7th October 1993). The investigator considered that the cardiac arrest was caused by failure to respond to therapy compounded with the patient's underlying heart disease.

This 78 year old female received azithromycin for 7 days for a bronchopneumonia caused by *E. coli*, though this should have excluded her from the protocol. Her pneumonia started on 9th August 1993 and azithromycin treatment started on 16th August 1993, following an unsuccessful course of co-trimoxazole (sulphamethoxazole and trimethoprim). The patient had a history of bronchiectasis and asthma and was receiving beclomethasone, digoxin and prednisone at study entry. She was treated with azithromycin for 7 days (3 intravenous, 4 oral) with improvement of her clinical symptoms and eradication of the baseline pathogen. However, her condition deteriorated on 22nd August 1993. This was attributed to a new infection with *Pseudomonas aeruginosa*, first cultured from a sputum sample taken on the 19th August. Azithromycin was discontinued because of this infection, deemed an intercurrent illness by the investigator, and intravenous treatment with amoxycillin and gentamicin was started. Although the *Pseudomonas* was eradicated, the patient's respiratory function decreased rapidly and she died of respiratory failure secondary to her infection on 28th August 1993.

This 73 year old male entered the study on 13th September 1993 with a primary diagnosis of acute exacerbation of chronic bronchitis. The onset date was three days before and ciprofloxacin, chloramphenicol and co-trimoxazole were recorded as previous therapies. The patient had a 15 year history of chronic obstructive pulmonary disease and was oxygen dependent. He also had a history of adenocarcinoma of the right upper lobe (treated by surgery and radiotherapy two years previously), left foot drop, eczema and a malignant bladder polyp. Sputum culture at baseline yielded a haemolytic group B streptococcus, which the investigator regarded as the primary pathogen, and a methicillin resistant *Staphylococcus aureus (MRSA)* which was initially thought to be a contaminant. The patient was treated with IV azithromycin for 4 days with eradication of the streptococcus but clinical failure. The MRSA was cultured again on the third day of treatment (15th September) and the investigator changed its designation to pathogen, recording pneumonia due to *S. aureus* as a concurrent disease at baseline. Azithromycin was discontinued due to lack of efficacy and vancomycin substituted. The investigator recorded slow but steady improvement and the patient was transferred to a convalescent home on 4th October 1993. The investigator later heard that the patient had died of chronic obstructive pulmonary disease the following day, 19 days after discontinuing azithromycin.

(Azithromycin)

death

This 22-year-old white female inpatient in Costa Rica with a history of primary pulmonary hypertension was treated with azithromycin for community acquired pneumonia. Study drug was administered intravenously at a dose of 500 mg daily

from March 2 to 6, 1993 and orally at a dose of 250 mg twice daily (total daily dose of 500 mg) from March 7 to 9, 1993. On March 10, 1993 the patient died due to cardiopulmonary arrest secondary to massive pulmonary embolism, confirmed by autopsy. The patient's medical history is negative except for primary pulmonary hypertension of unknown etiology that was diagnosed one year prior to entering the study. Concomitant medications included cimetidine and aluminum magnesium suspension.

(Azithromycin)

death

This 26-year-old white female inpatient in Costa Rica was treated with azithromycin for community acquired pneumonia. Study drug was administered intravenously at a dose of 500 mg daily from October 26 to 30, 1993. On the evening of October 30, this patient developed adult respiratory distress syndrome and acute respiratory failure. She died on the morning of October 31. Past history obtained at the time of admission was unremarkable and the only concomitant therapy was dextromethorphan for cough, given from October 26 to 30. Following this patient's death, the patient's mother indicated to the investigator that the patient had been using crack cocaine on and off prior to her hospitalization. At the time of admission, however, the patient had specifically denied substance abuse. The investigator indicated that the use of cocaine was becoming an increasing problem in Costa Rica and that at least two patients had died within the past year in the hospital with adult respiratory distress syndrome secondary to cocaine abuse. No serum or fluid specimens were available for this patient for illicit drug testing, and the family denied permission for an autopsy.

(Azithromycin)

death

This 57-year-old male inpatient in Costa Rica was treated with azithromycin for community acquired pneumonia. Study drug was administered intravenously at a dose of 500 mg daily from November 11 to 13, 1993. On November 14, the patient developed chest pain and cardiopulmonary arrest following a morning shower. Attempts at resuscitation were unsuccessful and the patient died. Autopsy revealed an acute myocardial infarction and underlying coronary artery disease. Medical history includes long standing deafness secondary to occupational noise exposure and resection of a benign thyroid nodule in 1963. Concomitant therapies included diclofenac (one dose IM on November 13), albuterol inhaler, magnesium sulphate, methylprednisolone, acetaminophen and an antihistamine/cough preparation.

JAN 29 1997

NDA 50,733

DATE of SUBMISSION
Feb. 5, 1996

Azithromycin for intravenous injection
Original NDA, new route of administration

Clinical Pharmacology and Biopharmaceutics Review

SPONSOR: Pfizer Central Research.
Eastern Point Road
Groton, CT 06340

REVIEWER: HE SUN, Ph.D.

I. SYNOPSIS

One pivotal study, #93CE33-0625A, shows that when patients hospitalized with community-acquired pneumonia were treated with 500 mg daily intravenous azithromycin (2 mg/ml infused over 1 h) for 2 to 5 days, the mean C_{max} was 3.6 μg/ml, the mean C_{24} of the final dose was 0.20 μg/ml and the mean AUC_{24} was 9.6 μg.h/ml. Another pivotal study, 95CK33-0674, shows that when azithromycin 500 mg was administered daily intravenously to healthy volunteers (1 mg/ml infused over 3 h) for 5 days, after the start of the final infusion dose, the mean C_{max} was 1.16 μg/ml, the mean C_{24} was 0.18 μg/ml and the mean AUC_{24} was 8.03 μg.h/ml.

Eight supportive studies indicated that when azithromycin was administered daily intravenously for 5 to 10 days to healthy volunteers in doses of 500 to 2000 mg infused over 1 to 3 hours, there was virtually no change in C_{max}, but there was a 40-61% increase in AUC_{24} on Day 5 or Day 10 relative to Day 1, reflecting 1.75 to 3 fold increase in C_{24}. Pharmacokinetics of azithromycin following single doses of 1000 mg to 4000 mg (1 mg/ml) infused over 2 hours in healthy volunteers, are linear and dose proportional. The mean disposition half-life following intravenous dosing in healthy volunteers ranged from 65 to 72 hours. The high overall values for apparent steady-state volume of distribution (33.3 L/kg) and plasma clearance (10.2 ml/min/kg) suggest that the prolonged half-life is due to extensive tissue uptake and subsequent release of drug from tissues. Approximately 14% of the administered dose was recovered in urine over the 24 hours dosing interval following daily dosing for 5 days with 500 mg azithromycin infused over 1 hour. Healthy volunteers tolerated up to 1000 mg daily azithromycin with the maximum concentration being 2.0 mg/ml for 10 days.

II. RECOMMENDATION

Two pivotal studies, #93CE33-0625A and #95CK33-0674, are acceptable. Both studies support that the IV formulation can be given at 500mg dose as 1 mg/ml, 3-hours infusion, or 2 mg/ml, 1-hour infusion produces acceptable plasma azithromycin concentrations and is tolerable.

Please convey **SPECIFIC COMMENTS** #5 on page 9 and **COMMENTS ON LABELING** on page 10 to the sponsor.

TABLE OF CONTENTS:

III. BACKGROUND

The sponsor submitted this original NDA for Zithromax (azithromycin for intravenous injection) for the treatment of patients with community-acquired pneumonia (CAP) or pelvic inflammatory disease (PID) who require initial intravenous antibiotic therapy.

Ten (10) clinical pharmacokinetics/ pharmacodynamics studies were submitted to support the new formulation. In addition, 7 supportive studies (listed below) were previously submitted to other NDA's. These studies used IV azithromycin formulation as the reference for calculating the absolute bioavailability of other azithromycin formulations in adult subjects:

Study #	NDA#	Date Submitted
056	50-670,	December 12, 1994
036	50-670,	November 30, 1994
049	50-670,	August 30, 1994
045	50-670,	August 30, 1994
046	50-711,	February 15, 1994
057	50-693,	December 29, 1993
006	50-670,	April 11, 1990

IV. DRUG FORMULATION

The drug product compositions are listed on page 3

B. Drug Product [Azithromycin For Injection (100 mg/mL)]

Composition

Each vial contains azithromycin dihydrate equivalent to 500 mg of azithromycin. Each vial also contains: anhydrous citric acid (as buffer), sodium hydroxide (buffering agent),

The quantitative composition of azithromycin for injection is:

Ingredient	Grade	mg/vial
✓Azithromycin Dihydrate for Parenteral Use	Pharm	
✓Citric Acid, Anhydrous	USP	
✓Sodium Hydroxide	NF	

Total (liquid weight)

Total (dry weight)

a: Is added as the active ingredient and is introduced on actual assay. Equivalent to 500 mg azithromycin based on a theoretical potency of 95.4% of azithromycin.
b: Is added as a buffer.
c: Is added to adjust the pH of the solution.
d: Is used as a solvent which is evaporated during the manufacturing process.
e: This is the liquid weight in the vial prior to lyophilization. There is sufficient excess solution present to allow withdrawal of 500 mg of azithromycin in 5 mL solution.
(f) This is the dry weight in the vial after lyophilization. There is sufficient excess solution present once reconstituted to allow withdrawal of 500 mg of azithromycin in 5 mL solution.
(g) Used to provide an inert atmosphere during the manufacturing process.

Manufacturing and Packaging

Azithromycin for injection will be manufactured, labelled and packaged at the following site:

V. SUMMARY of STUDIES

A. PIVOTAL STUDIES

1. Protocol 93CE33-0625A

Title: Pharmacokinetics of IV azithromycin in hospitalized patients with community acquired pneumonia (Pfizer Central Research. U.S.)

The objective of this study was to characterize the pharmacokinetics of azithromycin following 1 hour infusions of 500 mg azithromycin (2mg/ml) QD for 2 to 5 days to hospitalized patients with community acquired pneumonia. A total of twelve consenting patients, ranging in age from 20 to 94 years entered and completed this study. Patients received 2 to 6 doses of IV azithromycin. Blood samples were collected at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours following the start of the last azithromycin IV dose of 500 mg. Plasma concentrations of azithromycin were determined using an HPLC-EC method.

Azithromycin pharmacokinetic data were evaluated over the dosing interval following the last IV dose in 11/12 patients. The mean±SD values for C_{max} and AUC_{24} were, respectively, 3.6±1.6 μg/ml and 9.6±4.8 μg.h/ml. The mean±SD trough azithromycin value after the final infusion dose, C_{24}, was 0.20±0.15 μg/ml. The mean azithromycin plasma concentration profile shows a rise up to the C_{max} followed by a rapid fall in plasma levels within one hour following the end of the 1-hour infusion. The azithromycin infusions were well tolerated.

2. Protocol 95CK33-0674

Title: Multiple dose pharmacokinetics of azithromycin following 3-hour intravenous infusion for 5 days in healthy volunteers (Pfizer Central Research. U.S.)

This study was designed as a randomized, open, placebo-controlled study to evaluate the IV pharmacokinetics and toleration of 500 mg azithromycin daily for 5 days, infused as 1 mg/ml over 3 hours, in healthy male volunteers. Twenty-three subjects, 18-38 years old, randomized in a 2:1 ratio into azithromycin (N=16) and placebo (N=7) treatment groups, completed the study. Plasma samples were collected on treatment Days 1 and 5 and plasma azithromycin levels were determined using an HPLC-EC assay.

Pharmacokinetic parameters, C_{max}, AUC_{24}, and C_{24} and their Day 5/Day 1 ratios were determined on Days 1 and 5 for each subject. On Day 1, the mean±SD values (N=16) for C_{max}, AUC_{24} and C_{24} were, respectively, 1.08±0.13 μg/ml, 5.00±0.64 μg.h/ml and 0.06±0.01 μg/ml. On Day 5, the mean±SD values (N=16) for C_{max}, AUC_{24} and C_{24} were, respectively, 1.16±0.14 μg/ml, 8.03±0.86 μg.h/ml and 0.18±0.02 μg/ml. The Day 5/Day 1 parameter ratios for C_{max}, AUC_{24} and C_{24} were 1.08±0.12, 1.61±0.11 and 3.06±0.56, respectively. Although there was only an 8% increase in C_{max} between the first and fifth infusions of azithromycin, there was a 61% increase in AUC_{24} as a consequence of the threefold increase in C_{24} over the five doses. The mean azithromycin plasma concentration profile shows a rise up to the C_{max} followed by a rapid fall in plasma levels within one hour following the end

of the 3-hour infusion. Daily intravenous administration of azithromycin 500 mg for five consecutive days was well tolerated.

C. SUPPORTIVE STUDIES

1. Protocol 066-234

Title: A single blind, placebo controlled study to assess the safety, toleration and pharmacokinetics of five daily doses of 500 mg of intravenous azithromycin (Pfizer Central Research - Non U.S.).

Pharmacokinetics and toleration of 500mg azithromycin infused as 1mg/ml over 1 hour daily for 5 days were investigated in 17 healthy male volunteers. Subjects were randomized into azithromycin (N=13) and placebo (N=4) groups.

The mean±SD AUC_{24} following the first and last of the five daily doses were 4.83±0.51 μg.h/ml and 6.78±0.75 μg.h/ml, respectively; the mean AUC ratio for the last to first dose was 1.41. The mean±SD of C_{max} on Days 1 and 5 were comparable (2.69±0.36 and 2.64±0.29 μg/ml, respectively); the mean C_{max} ratio was 0.99. The mean±SD trough plasma concentrations (C_{24}) after the start of the 1st and 5th infusion doses were 0.05±0.01 and 0.11±0.02 μg/ml, respectively (C_{24} Ratio: 2.2). The amounts of azithromycin excreted in urine during the 24-h period after the first and last IV infusions corresponded to 10.5±1.0% and 14.3±3.1% of the administered daily dose, respectively.

Although there was virtually no change in C_{max} after the fifth infusion dose relative to the first, there was a 40% increase in AUC_{24} of azithromycin arising from the 2-fold rise in the trough plasma concentrations of azithromycin (C_{24}).

2. Protocol 066-217

Title: A single blind, placebo controlled study to assess the safety, toleration and pharmacokinetics of multiple-dose, intravenous azithromycin (Pfizer Central Research - Non U.S.)

Pharmacokinetics and toleration of 500mg azithromycin infused as 10 mg/ml over 1 hour daily for 5 days were investigated in 17 healthy male volunteers (20 to 38 years old). Subjects were randomized into azithromycin (N=12) and placebo (N=5) groups.

The first 7 subjects receiving azithromycin 10 mg/ml experienced pain at the infusion site and withdrew from the study after the second infusion. Of these remaining 5 subjects, three subjects received 2.5 mg/ml on Day 0 and 1.67 mg/ml on Days 1 and 2, and two subjects received 0.5 mg/ml each day. Blood and urine samples were obtained up to 24 hours after the start of the infusion on Days 0 and 2. Plasma and urine samples were assayed for azithromycin using HPLC with EC detection.

Results show that although, there was only a 6% increase in C_{max} after the third infusion dose relative to the first, there was a 40% increase in AUC_{24} of azithromycin arising from the 1.75-fold rise in the trough plasma concentrations of azithromycin (C_{24}). Azithromycin infusions of 0.5 to 2.5 mg/ml over 1 hour were well tolerated but the 10 mg/ml infusion produced unacceptable injection site reactions.

3. Protocol 066-058

Title: A multiple-dose study with fixed doses of intravenous azithromycin and increasing concentrations of infusate (Pfizer Central Research-U.S.)

Dermatologic effects and toleration at the injection site were assessed by increasing infusion concentration (1,2.5,4, and 5 mg/ml, N=5 to 6 for azithromycin, N=2 for placebo per group) of 2000 mg IV azithromycin administered over 1 hour daily for 6 days. The injection site was clinically inspected and rated on a ten-point visual analog scale, with each pharmacokinetic blood draw on Days 1 and 10.

There were no apparent differences in AUC_{0-24} and C_{max} values among the four treatment groups on Day 1. The consecutive daily dosing resulted in 54% and 57% increase in the mean Day 10/Day 1 AUC_{24} ratio for the 1 mg/ml and 2.5 mg/ml groups, respectively. The prematurely terminated dosing plus the variability in administered doses and infusate concentrations make it difficult to draw meaningful conclusions for the 5 mg/ml and 4 mg/ml groups. Local reactions of irritation, pain, tenderness, swelling, warmth and rash appeared to be increased in frequency compared with placebo and were greatest during the infusion. Concentrations of 4 mg/ml and 5 mg/ml required discontinuation of therapy.

4. Protocol 066-044

Title: An escalating single-dose study to assess the gastrointestinal effects of intravenous azithromycin (Pfizer Central Research U.S.)

This double-blind, placebo-controlled, parallel group study was to evaluate the dose dependency of intravenous azithromycin doses to effects on the gastrointestinal tract. Twenty-three healthy, adult males, 18 to 43 years old, were divided into three groups of eight (6 azithromycin, 2 placebo) and were randomized to receive an intravenous infusion (1 mg/ml over 2 hours) of 1000 mg, 2000 mg, or 4000 mg azithromycin or placebo. Six subjects received 1000 mg, 6 subjects received 2000 mg, and 5 subjects received 4000 mg. Blood samples were collected from each subject up to 240 hours after the start of the intravenous infusion.

The pharmacokinetics of azithromycin are linear and dose proportional across the dose range of 1000 to 4000 mg. (See table below):

	IV Azithromycin				
	1000mg (N=6)	2000mg (n=6)	3000mg (n=1)	4000mg (n=5)	overall (N=18)
AUCinf (ug.hr/ml)	23.40	45.58	62.42	82.06	
Cmax (ug/ml)	3.110	6.837	9.150	9.910	
Tmax(hours)	1.9	1.8	1.5	1.05	
Kel (hr-1)	0.0107	0.0096	0.0090	0.0100	0.0100
T1/2(hours)	64.8	72.2	77.3	69.3	69.3
Clt(ml/min/kg)	10.10	9.54	10.47	10.99	10.18
Vdss(L/kg)	30.1	30.5	43.5	38.3	33.3

The incidence of gastrointestinal side effects (abdominal pain, abdominal cramping, and nausea) in

this study was generally related to the dose administered.

5. **Protocol 93CE33-0618A**

Title: Pharmacokinetics of IV azithromycin in hospitalized patients with community acquired pneumonia (Pfizer Central Research - U.S.)

The objective of this study was to characterize the pharmacokinetics of azithromycin following 3 hour infusions of 500 mg azithromycin (1 mg/ml) QD for 2 to 5 days to hospitalized patients with community acquired pneumonia under Protocol 93CE33061. A total of six consenting patients, 48-89 years old, received 2 to 5 doses of IV azithromycin (1 mg/ml).

The azithromycin pharmacokinetic data were evaluated over the dosing interval following the last IV dose in 5/6 patients. The mean±SD values for C_{max}, T_{max} and AUC_{24} were, respectively, 1.6±0.3 μg/ml (Range: μg/ml), 1.8 ± 0.8 hr (Range: hr) and 9.3±1.6 hr.μg/ml (Range: μg/ml). The mean C_0 and C_{24} values were, respectively, 0.15 μg/ml (Range: μg/ml) and 0.26 μg/ml (Range: μg/ml).

Intravenous azithromycin pharmacokinetics in this small clinical study (N=5) exhibited wide variability across subjects. The coefficients of variation for C_{max} and AUC_{24} were relatively smaller at 21.0% and 17.7%, respectively, than T_{max}, C_0 and C_{24} with coefficients of variation of 46%, 36.3% and 48.8%, respectively.

6. **Protocol 066-052** (data referenced but not reviewed in detail)

Title: The effects of increasing infusate concentrations on toleration of intravenous azithromycin in healthy volunteers (Pfizer Central Research-U.S.)

The study was a crossover design in three groups of azithromycin and placebo with six subjects per group. Subjects initially randomized to 1 mg/ml received a second infusion of 5 mg/ml, those who received 2 mg/ml received 4 mg/ml, those who received 5 mg/ml received 1 mg/ml, and those who received placebo continued to receive placebo during the second phase of treatment. Twenty-four healthy male volunteers, 19 to 41 years old, were enrolled and completed the study. The first and second phases of treatment were separated by a minimum of 17 days.

There was no clear association between azithromycin infusion concentration and the number of subjects experiencing discomfort and there was no association between duration of discomfort and infusion concentration. There were no apparent trends in Doppler readings that might be associated with changes in venous flow rates at any azithromycin infusion concentration. Mean serum concentrations of azithromycin immediately following infusion ranged from μg/ml.

7. **Protocol 066-225** (data referenced but not reviewed in detail)

Title: Single blind, placebo controlled parallel group study to compare the safety and toleration of

multiple dose intravenous azithromycin and erythromycin lactobionate (Pfizer Central research-Non U.S.)

The 500 mg intravenous azithromycin infused daily over 2 hours (0.5 mg/ml, N=12) or 1 hour (1mg/ml, N=8) for 3 days were compared with that of 500 mg intravenous erythromycin lactobionate infused three times daily over 1 hour, for 3 days (N=4). Following cessation of erythromycin dosing because of a high incidence of adverse events in the first 4 subjects, the remainder 8 subjects who had been assigned to receive erythromycin were transferred to a new group and received 1 mg/ml azithromycin infused daily over 1 hour. Venous toleration was assessed by inspection of the injection site and the vein used for the infusion was inspected for irritation and erythema every 15 minutes during infusion, and 15, 30 and 60 minutes after the end of the infusion. If irritation was associated with the infusion then the inspections were to be repeated 1.5, 2, 3, 4, 6, 8 and 10 hours after infusion commenced, until the visible signs of irritation had disappeared. Discomfort was assessed by the subjects at the same times as local irritation on a ten-point scale.

The results of this study indicate that intravenous azithromycin and erythromycin are both well tolerated locally. Azithromycin dosage regimens of 0.5 mg/ml infused over 2 h and 1 mg/ml infused over 1 h were both well tolerated.

8. Protocol 066-226A (data referenced but not reviewed in detail)

Title: Single blind placebo controlled study to investigate the safety and toleration of multiple dose intravenous azithromycin (Pfizer Central Research-Non U.S.).

This was a single blind, within-subject, placebo-controlled study in which nine healthy male volunteers, 18 to 25 years old, were randomized to receive 500 mg azithromycin intravenously over a two-hour period at concentrations of 0.5 mg/ml (N=5) or 1 mg/ml (N=4). The objective was to compare the safety and toleration of intravenous azithromycin administered daily for two days at these two concentrations. Subjects were treated once daily for two days with infusions of active treatment (azithromycin) in one arm and placebo into the other arm. Local irritation and discomfort were assessed every 15 minutes during the infusion and 15, 30, and 60 minutes after infusion. If irritation resulted from the infusion, further assessments of irritation were to be made 1.5, 2, 3, 4, 6, 8, and 10 hours after the start of infusion, until visible signs of irritation had disappeared. Subjects assessed discomfort on an ascending ten-point scale.

Intravenous azithromycin was well-tolerated both locally and systemically; toleration was similar for azithromycin concentrations of 0.5 mg/ml and 1 mg/ml when infused over 2 hours.

VI. SPECIFIC COMMENTS

Comments need not to be conveyed to the sponsor

1. Based upon all 10 studies, it is concluded that the GI tract side effect (the major side effect) is dose related while the infusion site reaction is infusate concentration dependent. Healthy

volunteers tolerated up to 1000 mg daily azithromycin with the maximum concentration being 2.0 mg/ml for 10 days.

2. The two 500 mg dose regiments, i.e., 2 mg/ml, 1 hour infusion and 1 mg/ml, 3 hour infusion, produce acceptable plasma azithromycin concentrations. The C_{max} for 2 mg/ml/1hour regimen is 3 times higher than that of 1 mg/ml/3hour infusion regiment (3.6 μg/ml and 1.16 μg/ml, respectively) while the C_{24} and AUC_{24} values are basically the same (0.2 μg/ml and 0.18 μg/ml for C_{24}, and 9.6 μg.h/ml and 8.03 μg.h/ml for AUC_{24}, respectively).

3. It was observed that there was virtually no change in C_{max}, but there was a 40-61% increase in AUC_{24} on Day 5 or Day 10 relative to Day 1, and 1.75 to 3-fold increases in C_{24} when azithromycin was administered daily intravenously for 5 to 10 days to healthy volunteers in doses of 500 to 2000 mg infused over 1 to 3 hours. From a pharmacokinetics standpoint, for a drug described with a typical 2 compartment model and a very large volume of distribution, these results are acceptable.

4. The inter-subject variability in study #93CE33-0625A and study #93CE33-0618A is much higher than that observed in any other studies. This large variation may be due to the large age range in these two studies compared to in other studies (in which, healthy male volunteers were enrolled).

   In regard to the effect of demographic variables (gender, age, race and body weight) on pharmacokinetic parameters, it can be seen in Figure 2, 3 and 4 of study 93CE33-0625A that AUC_{24} is well correlated with age while C_{max} and C_{24} are age independent. it should be pointed out that C_{max} values are mainly infusion rate and Vd dependent, and a inconsistent infusion rate among subjects was demonstrated by the inconsistent T_{max} values (ranged from 0.5 to 3 hours). Therefore, C_{max} is less sensitive to demographic variables. On the other hand, AUC_{24} is mainly dose and CL dependent. When a 500 mg dose is consistently administered, the variation in AUC_{24} reflects the variation in CL. This observation suggest that CL is inversely correlated with age (also, see Comments on Labeling).

Comments need to be conveyed to the sponsor

5. AUC_{24} data from study 93CE33-0625A suggest that CL is inversely correlated with age. However, no solid conclusion could be made based on the limited data of 11 patients. Does the sponsor has data availiable for examining if age has effect on azithromycin pharmacokinetics?

V. COMMENTS on LABELING

1. On page 5, Clinical Pharmacology Section, paragraph one:

   (1). The sponsor should indicate that the pharmacokinetic parameter values described are those of last dose following 2-5 days single daily drug administration.

(2). The Standard Deviation (SD) should be given for each pharmacokinetic parameter. This information is needed for comparing PK parameters between healthy volunteers and patients.

(3). All numbers should have consistent format.

2. For the plasma concentration table on page 5, the title of the table should read as "plasma concentration (ug/ml) after the last daily dose of 500 mg azithromycin iv infusion."

3. The following paragraph should be added immediately following the pharmacokinetic table:

The average CL_t and V_d values were 10.18 ml/min/kg and 33.30 L/kg, respectively, in 18 normal volunteers receiving 1000-4000 mg doses giving as 1 mg/ml over 2 hours.

4. In Dosage and Administration Section (page 15), a new paragraph to describe how the 500 mg dose will be administered, i.e. the two dose regimens, 2 mg/ml/1 hour infusion, and 1 mg/ml/3 hour infusion, should be added.

The following paragraph also should be added: "The recommended infusate concentration and rate of infusion for ZITHROMAX (azithromycin for intravenous injection) is either 1 mg/ml over 3 hours or 2 mg/ml over 1 hours."

1/29/97

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. F. Pelsor

CP/B Briefing: Date Jan. 23, 1997.
cc:
NDA 50,733
HFD-520 (Clinical),
HFD-340 (Viswanathan),
HFD-880 (Pelsor, Sun)
HFD 880 Div. File- NDA 50,733 (azithromycin)
HFD 850 Drug File (Mira Millison)

Clinton 520

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, HFD-520

NDA#: 50-733 (000)

SPONSOR: Pfizer Inc.
235 East 42nd Street
New York, NY 10017

AUTHORIZED REPRESENTATIVE:
Margaret A. Longshore, Ph.D.
(212) 573-2556

DRUG NAME: Zithromax (Azithromycin for injection)

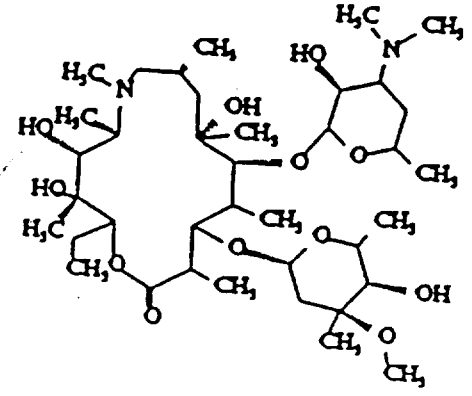
CATEGORY: Macrolide Anti-microbial [Subclass: Azalide]

COMPOSITION:

Quantitative Composition of the Dosage Form.	
INGREDIENTS	*AMOUNT (mg/vial)*
Azithromycin Dihydrate*	
Citric Acid, Anhydrous (USP)	
Sodium Hydroxide (NF)	
Total*** (liquid weight) (dry weight)	

* => Equivalent to 500 mg Azithromycin at a potency of 95.4%
** => Used as solvent and evaporated during manufac. process
*** => Liquid weight: weight prior to lyophilization
Dry weight: weight in vial after lyophilization

STRUCTURAL FORMULA:



RELATED SUBMISSIONS: IND #s
NDA #s 50-670; 50-693; & 50-710
DMF #s

NUMBER OF VOLUMES: 10

INFORMATION CONVEYED TO THE SPONSOR: YES (X), NO ( )

DATE CDER RECEIVED: 2/6/96

DATE ASSIGNED: 2/12/96

DATE REVIEW STARTED: 5/9/96

DATE 1st DRAFT COMPLETED:

DATE REVIEW ACCEPTED BY SUPERVISOR: June 24, 1996

REVIEW OBJECTIVES:
To review original NDA submitted in support of Zithromax (Azithromycin for intravenous (i.v.) injection) for the treatment of patients with Community-Acquired Pneumonia (CAP) or Pelvic Inflammatory Disease (PID).

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Adult patients would receive Azithromycin 500 mg as a single daily dose by the i.v. route for at least two days for community-acquired pneumonia and for one or two days for pelvic inflammatory disease. This i.v. therapy would be followed by azithromycin by the oral route at the discretion of the physician and in accordance with clinical response.

PRECLINICAL DATA:

TOXICOLOGY

I. A 14-Day intravenous toxicity study in Sprague-Dawley rats, (Study # 85-454-05), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: December, 1985.

This study was conducted to investigate the short term effects of the i.v. administration of azithromycin (citrate salt) in rats and to support a single dose pharmacokinetic studies in man. Four groups of rats (10/sex/group) were treated by i.v. injection with azithromycin. Group 1 (control) received 0.9% sodium chloride solution for 14 consecutive days. Groups 2 and 3 received azithromycin 10 and 20 mg/kg, i.v. for 14 days, respectively.

Group 4 was treated every other day at 20 mg/kg, i.v. for a total of seven doses to prevent any possible drug accumulation. On day 15, all treated and control animals were sacrificed and necropsied. Each rat was observed at least twice a day for mortality, changes in behavior indicative of toxicity. Body weight and food consumption were monitored and recorded. Serum chemistry, hematology, and urinalysis were obtained on each animal once prior to the start of dosing and on days 8 and 15.
RESULTS & CONCLUSIONS:
Azithromycin, administered i.v. to Sprague Dawley rats at 10 or 20 mg/kg/day for 14 consecutive days, and 20 mg/kg every other day for 7 doses, produced no adverse effects on food consumption, body weight gain, appearance or behavior. Serum chemistry, hematology, and urinalysis parameters analyzed were normal. In treatment groups, no significant changes were observed in the liver/body weight ratios. No gross or microscopic tissue changes attributable to drug treatment were observed. There was no evidence of elevated serum hepatic enzyme levels or of tissue phospholipidosis.
Comments: The dose levels selected in the study appeared low and the duration of study was also short, especially for the development of phospholipidosis. In a previous 4-week oral study (Study # 82-454-03), rats treated at 50, 100, and 200 mg/kg, developed hepatotoxicity (elevated SGPT, SGOT, SDH, & 5'NT) and phospholipidosis in a dose- and time-dependent fashion. However, significant reversibility was indicated following 3-week recovery period.

II. A 14-Day intravenous toxicity study in Sprague-Dawley rats, (Study # 85-454-45), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: April, 1990.

This study was conducted to verify the tolerance of S.D. rats for the fumarate salt of azithromycin when given i.v. for 2 weeks in order to support a single dose pharmacokinetic studies in man. Four groups of rats (10/sex/group) were treated by i.v. injection with the test compound. Group 1 (control) received 0.9% sodium chloride solution and Group 2 received 5 mg/kg azithromycin for 17 consecutive days and necropsied on day 18. Groups 3 and 4 received azithromycin 10 and 20 mg/kg, i.v. for 16 consecutive days, respectively and necropsied on day 17. Each rat was observed at least twice a day for mortality, changes in behavior indicative of toxicity. Body weight and food consumption were monitored and recorded starting one day before dosing. Serum chemistry, hematology, and urinalysis were obtained on each animal once prior to the start of dosing and again during week 3 of the study. Serum levels of azithromycin were measured in 4 rats/sex/dose at 0.25 and 24 hours post-dose on days 1 and 15 of

treatment. On days 17 or 18 after overnight fasting, all rats were sacrificed and major organs were inspected and weighed. Tissue samples were taken and processed for histopathology.
RESULT & CONCLUSIONS:
Azithromycin fumarate, administered i.v. to S.D. rats in doses of 5, 10 and 20 mg base/kg/day for 16-17 days, was well tolerated and had no untoward effect on body weight, food consumption, appearance or on overt behavior. Serum levels of drug at 0.25 and 24 hours following drug treatment on days 1 and 15, showed dose-dependent increases and were about 1.5 to 2-fold higher on day 15 vs day 1. There were no significant drug-related effects on clinical chemistry, hematology or urinalysis parameters. Phospholipidosis of the large intrahepatic bile duct epithelium was observed in 80% of the high-dose (20 mg/kg) animals, but did not occur in other tissues or at lower doses in this study.

III. A 1-Month intravenous toxicity study in Sprague-Dawley rats, (Study # 87-454-22), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: November, 1987.

This study was conducted to investigate the effects of azithromycin when administered i.v. to S.D. rats for 1 month in order to support a multiple dose i.v. administration in man. Four groups of rats (10/sex/group) were treated by i.v. injection with the test compound. Group 1 (control) received 0.9% sodium chloride solution. Groups 2, 3, and 4 received 20, 10, and 5 mg/kg/day azithromycin, respectively for 36 to 39 consecutive days.

Each rat was observed at least three times a day for mortality, changes in behavior and for signs of toxicologic effects. Body weight and food consumption were monitored and recorded prior to the start of dosing. Ophthalmoscopic examinations were performed on all rats once prior to the onset of treatment and again at the end of the study. Mydriasis was induced by instilling one drop of 1.0% tropicamide into each eye.

Serum chemistry, hematology, and urinalysis were obtained on each animal once prior to the onset of drug administration and again on days 18-19 and 30-33. Serum levels of azithromycin were measured in 3 rats/sex/dose at 1 and 24 hours post-dose on days 1, 15, and 36 of treatment. Another separate group of rats (9/sex/dose) were treated at either 0 or 20 mg/kg/day. Three rats/sex/dose were sacrificed, 24 hours after their last dose of drug, on days 2, 16, and 37. Blood samples and tissue specimens from the liver, kidney, spleen, lung, and lymph node were collected for the determination of azithromycin concentrations.

Following 36-39 days of dosing, all surviving rats were fasted overnight, and necropsied on days 37 to 40. All major organs including kidneys, heart, lung, pancreas, ovaries, spleen,

stomach, pituitary, adrenals, liver, brain, skin, eye, and left and right testis were inspected, weighed, and processed for histopathology.
RESULT & CONCLUSIONS:
Azithromycin administered i.v. in citrate solution to S.D. rats in doses of 5, 10 and 20 mg/kg/day for 36-39 consecutive days, had no effect on food consumption and body weight gain. No drug-related ocular changes were observed in any rat. There were no drug-induced changes in any serum chemistry, hematology, or urinalysis parameters. Serum concentrations of azithromycin were dose-related and showed no significant changes over the course of the study. Generally, there were little or no accumulation of azithromycin in the serum with daily doses. Splenic tissue concentrations in the animals at 20 mg/kg/day, was higher than hepatic tissue concentrations at all time points. Following 1, 15, and 36 daily doses, mean spleen concentrations were 84, 293, and 392 µg/g, respectively as compared to the mean liver concentrations of 56, 109, and 91 µg/g, respectively at the same time points. However, the mean concentrations of azithromycin in the liver and the spleen exceeded the mean concentrations in the serum by 490 to 2400-fold, respectively.
There were no drug-related alterations in liver, kidney or testis weights. Drug-related phospholipidosis was observed in the epithelium of the large bile ducts in all animals treated at high-dose levels, in 65% (13/20) mid-dose animals, and at the injection site in the tail of 1 high dose rat. There was no evidence of phospholipidosis at the 5 mg/kg/day dose level. Local perivascular granulomatous inflammatory reactions were reported at the tail injection sites in 10 to 30% of the rats in all treatment groups. This inflammatory phenomenon is believed to be due to drug-related local tissue irritation as none of these were seen in the controls.

IV. A 2-Week intravenous toxicity study in Beagle Dogs, (Study # 85-454-06), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: December, 1985.

This study investigated the short term effects of the i.v. administration of azithromycin (citrate salt) in beagle dogs and to support a single dose pharmacokinetics study in man. Twenty four beagle dogs (12 males and 12 females), were randomly divided into 4 groups of 3/sex/group. Group 1 (control) received 0.9% sodium chloride solution for 14 consecutive days. Groups 2 and 3 received azithromycin 10 and 20 mg/kg/day, i.v. for 14 days, respectively. Group 4 was treated every other day at 10 mg/kg, i.v. for a total of seven doses to prevent any possible drug accumulation as a result of the drug's long half-life. On day 15, all treated and control dogs were sacrificed and necropsied. Each

dog was observed several times daily, for mortality, changes in appearance and behavior indicative of toxicity. Body weight and food consumption were monitored and recorded. Electrocardiographic tracings, i.e., three bipolar limb leads, augmented unipolar leads, and chest leads were simultaneously recorded. Changes in blood pressure were also monitored on each dog two times prior to the first day of dosing and again during the second week of dosing. Complete clinical pathology profile - serum chemistry, hematology, and urinalysis were obtained on each animal twice pre-test and at necropsy. Blood samples were collected on days 2, 4, 6, 8, 10, and 12 for determination of SGOT, SGPT, ALP, SDH, and GGTP. The drug's plasma level was determined for all dogs at 0.25, 1, 4, and 24 hours post-dose on days 7, 13, and at necropsy. At necropsy, several major organs including kidneys, heart, lung, pancreas, ovaries, spleen, stomach, pituitary, adrenals, liver, brain, skin, eye, and left and right testis were inspected, weighed, and processed for histopathology.

RESULTS & CONCLUSIONS:

Azithromycin, in aqueous citric acid solution given to beagle dogs at 10 or 20 mg/kg/day, i.v., for 14 consecutive days and 10 mg/kg every other day for 7 doses, produced no untoward effects on food consumption, body weight gain, or on appearance or behavior. Occasional episodes of emesis and unformed stools occurred in the 10 and 20 mg/kg/day treatment groups. Mild increase in serum liver enzymes (SGPT, ALP, and SGOT) activity occurred in 2/3 females at high-dose levels. Serum alkaline phosphatase activity also gradually increased in one 10 mg/kg/day female. There were no serum enzyme changes in the dogs receiving 10 mg/kg every other day. All other serum chemistry, hematology, and urinalysis data in all dogs were unremarkable. The mean azithromycin plasma concentrations on day-7, 15 minutes post-dose were 2.3, 3.4, and 3.7 µg/ml for the 10 mg/kg every other day, daily 10 and 20 mg/kg dose levels, respectively. There were detectable azithromycin plasma levels in all dogs at 24 hours post-dose, an observation consistent with the long half-life. The data showed that all the animals were exposed to the drug in a dose-proportional manner and steady state was reached by day 7. Phospholipidosis was reported within the lamina propria of the gall bladder and germinal centers of the mesenteric lymph nodes of dogs receiving 20 mg/kg/day. Phospholipidosis did not occur in either of the 10 mg/kg groups. No other drug-related effects were noted.

V. A 2-Week intravenous toxicity study of Azithromycin in Beagle Dogs, (Study # 89-454-46), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: February, 1990.

This study was designed to establish the local and systemic tolerance of an i.v. formulation of the fumarate salt of azithromycin in S.D. rats when given for 2 weeks in order to support pharmacokinetic studies in man. Twenty four beagle dogs (12 males and 12 females), were randomly divided into 4 groups of 3/sex/group. Group 1 (control) received 0.9% sterile saline solution for 15 consecutive days. Groups 2, 3, and 4 received azithromycin 5, 10, and 20 mg/kg/day, i.v. for 15 days, respectively. On day 16, all treated and control animals were fasted, sacrificed, and necropsied. Each dog was observed several times daily for mortality, changes in appearance and behavior indicative of toxicity. Body weight and food consumption were monitored and recorded twice prior to treatment initiation and then on days 1, 5, 8, 12, 15, and 16 of the study.
Electrocardiographic tracings consisting of the three bipolar limb leads, augmented unipolar leads, and chest leads were simultaneously recorded. Changes in blood pressure, heart rate, respiration rate, and rectal temperature were also monitored on each dog twice prior to the first day of dosing and again at one hour post-dose on days 1, 3, 9, and 11.
A complete clinical pathology profile was obtained on each animal twice pre-test and at necropsy. Blood samples were collected on days 2, 4, 6, 8, 10, and 12 for determination of SGOT, SGPT, ALP, SDH, and GGTP. The drug's plasma level was determined for all dogs at 0.25 and 24 hours post-dose on days 1 and 15. At necropsy, several major internal organs including kidneys, heart, lung, pancreas, ovaries, spleen, stomach, pituitary, adrenals, liver, brain, skin, eye, and left and right testis were inspected, weighed, and processed for histopathology.
RESULTS:
Azithromycin fumarate, administered i.v. to beagle dogs at 0, 5, 10 or 20 mg base/kg/day for 15 consecutive days, produced no untoward effects on food consumption, body weight gain, or on general appearance or behavior. No changes in serum liver enzyme activity were observed in any animal. Serum drug levels were shown to be dose-related. Electrocardiograms and blood pressures were all unremarkable. No treatment-related effects were detected in serum chemistry, hematology or urinalysis parameters. No effects on absolute or relative organ weights were evident, nor were there any compound-related pathological findings. None of the treated animals had any histological evidence of phospholipidosis. Injection site irritation due to repeated venipuncture was minimal to moderate in both control and treated animals. The results of the study indicated that 20 mg/kg/day is a No-Observable-Effect Level (NOEL) for the intravenous administration of azithromycin fumarate in beagle dogs.

VI. A One-Month intravenous toxicity study of Azithromycin in Beagle Dogs, (Study # 87-454-20), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: December, 1987.

This study investigated the effects of azithromycin when administered i.v. to beagle dogs for 1 month in order to support a multiple dose i.v. administration in man. Twenty four beagle dogs (12 males and 12 females), were randomly divided into 4 groups of 3/sex/group. Group 1 (control) received 0.9% sterile saline solution for 36 consecutive days. Groups 2, 3, and 4 received azithromycin 5, 10, and 20 mg/kg/day, i.v. for 36 days, respectively. On day 37, all treated and control dogs were fasted, sacrificed, and necropsied.

All dogs were observed at least three times daily, for mortality, changes in appearance and behavior related to drug toxicity. Individual body weights and food consumption were monitored and recorded weekly. Electrocardiographic tracings including the three bipolar limb leads, augmented unipolar leads, and chest leads were simultaneously recorded and changes in blood pressure were also monitored twice prior to the start of dosing and on study day 23. Ophthalmoscopic examinations were performed once pretest and again on study days 26-31. Complete clinical pathology profile - serum chemistry, hematology, and urinalysis were obtained on each animal twice pre-test and on days 16 and 30. Blood samples were collected for determination of several serum chemistry and hematologic parameters including SGOT, SGPT, ALP, SDH, and GGTP.

Another group of beagle dogs, 3/sex/dose, receiving azithromycin at doses of 0, 5, 10, and 20 mg/kg/day, i.v. for 36 consecutive days were sacrificed on day 37. Blood samples were collected at 1 and 24 hours post-dose on days 1, 15, and 29, and again on day 37. Tissue samples, such as the liver, spleen, kidneys, lung, and mesenteric lymph nodes were obtained for the determination of azithromycin serum and tissue concentrations. Following the 37 days of dosing, all surviving dogs were fasted overnight, and necropsied. Samples from the kidneys, heart, lung, pancreas, ovaries, spleen, stomach, pituitary, adrenals, liver, brain, skin, eye, and left and right testis were obtained, inspected, weighed, and processed for histopathology.

RESULTS & CONCLUSIONS:

Azithromycin citrate salt given to beagle dogs in doses of 0, 5, 10 and 20 mg/kg/day, i.v., for 1 month (36 days), was well tolerated. All dogs appeared clinically normal and showed no remarkable changes in EKG and blood pressure. No drug-induced ocular lesions were identified during the ophthalmoscopic examinations. Food consumption was not affected. Clinical pathology data showed that SGPT increases occurred in 66% of the high dose animals among which one dog showed a slight increase in serum alkaline phosphatase activity. There was no serum enzyme

changes at the 10 mg/kg/day dose level. Slight SGPT elevations were also noted in one low dose and one control animal.
The mean serum concentrations of azithromycin were proportional to dose level. At 1 hour post-dose, the mean serum concentrations were 1.8 to 2.2-fold higher at the 10 mg/kg/day dose and 3.0 to 4.2-fold higher at the 20 mg/kg/day dose level compared to the 5 mg/kg/day. The serum concentrations at 24 hours post-dose were 2.3 to 3.0-fold higher at the 10 mg/kg/day dose and 4.5 to 5.0-fold higher at the 20 mg/kg/day dose level compared to the 5 mg/kg/day, respectively. Between day 1 and 15, the serum concentrations at 1 hour post-dose increased 1.4, 1.3, and 1.2-fold and those at 24 hours increased 3.4, 2.7, and 3.7-fold, respectively, at the 5, 10, and 20 mg/kg/day dose levels. On day-29, serum concentrations were not higher than those on day 15, suggesting that steady state serum concentrations were achieved by day 15.
Tissue concentrations of azithromycin were higher in the spleen than in the liver, with mean spleen concentrations of 99, 525, and 1450 µg/g in the 5, 10, and 20 mg/kg/day dose group, respectively. Mean liver concentrations were 45, 180, and 565, respectively. No sex-related differences were observed in azithromycin tissue concentrations. The data also showed that tissue concentrations were much higher in spleen and liver than in the serum. Tissue-to-serum concentration ratios ranged from fold.
No treatment-related changes were seen grossly and the absolute and relative organ weights of drug-treated dogs were similar to that in controls. Prominent histological changes observed were the presence of phospholipidosis at the high dose: minimal to mild in the large bile ducts of 100%; minimal in the gall bladders of 66%, tonsils, 33% and mesenteric lymph nodes, 17%. One 10 mg/kg dog also showed minimal phospholipidosis in the large bile ducts. No evidence of phospholipidosis at 5 mg/kg/day was seen in the dog.

VII. An acute intravenous irritation study in albino rabbits, (Study # 88-454-39), GLP, Conducted at Drug Safety Evaluation Department, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: November, 1988.

This study was designed to investigate, in the rabbit, the gross and microscopic irritating potential of azithromycin in solution as compared to that of normal saline vehicle. Three male and three female New Zealand White rabbits, each weighing about 3.5 kg, were used for the study. A single dose of 1 ml/kg of 1% solution of azithromycin fumarate was injected into the marginal ear vein of 6 albino rabbits. An equal volume of normal saline was similarly administered to each animal in the opposing ear as control. The animals were sacrificed 24 or 48 hours after dosing. All animals were monitored for any clinical signs of toxicity

throughout the study. Food consumption and changes in body weights were monitored on daily basis. All ears and injection sites were evaluated once daily for gross tissue changes including discoloration, reddening, and/or edema. The intensity of these changes was graded (subjectively) as minimal, mild, moderate, or marked. Three rabbits were sacrificed at 24 hours post-dose and the remaining 3 were sacrificed at 48 hours post-dose. All ears were removed entirely and fixed in 10% buffered formalin. Sections of the ears were prepared for microscopic examination.
RESULTS & CONCLUSIONS:
All rabbits were reported to be asymptomatic throughout the test period, and there was no adverse effects on food consumption or body weight. No significant gross or microscopic differences were reported in the changes observed in veins injected with azithromycin solution or with normal saline. A consistent gross tissue change reported was minimal perivascular reddening that appeared to be confined to the point of injection or extended several mm along the vein; changes which can be attributed to the trauma of the injection. The changes noted microscopically included minimal to moderate perivascular hemorrhage, minimal or mild edema, minimal to moderate focal phlebitis and, in only two cases, focal thrombosis were reported. Therefore, the gross and microscopic tissue changes produced following the i.v. administration of 10 mg/kg of the azithromycin solution indicated that azithromycin solution was minimally irritating to the marginal ear vein of the rabbit.

VIII. In-Vitro Hemolysis and Compatibility Evaluation, (Study # CP-62,993), Conducted at Drug Safety Evaluation Department - Clinical Pathology, Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340. Study Date: August, 1985.

This study evaluated the hemolytic potential of azithromycin by the in-vitro method using human uncoagulated blood and whole blood. Compatibility of azithromycin with human serum and plasma was also evaluated.
Hemolysis Evaluation: A 10 mg/ml solution of azithromycin base was added in the ratio of 1:1, 1:10, 1:20, and 1:100 to normal human uncoagulated and whole blood. Normal saline was added as a vehicle control in a 1:1 ratio to the uncoagulated and whole blood and another 2 ml sample of uncoagulated and whole blood served as controls. The samples were processed accordingly and the plasma and serum were observed for the presence of hemolysis. Observations were made at room temperature hourly for 6 hours. All dilutions were refrigerated overnight then allowed to return to room temperature and again observed for hemolysis at 24 hours.
Compatibility Evaluations: The 10 mg/ml solution of azithromycin base was added in the ratio of 1:1, 1:10, 1:20, and 1:100 to normal human serum and plasma. Normal saline was added in a 1:1

ratio to 0.5 ml of serum and plasma as a vehicle control and a 1.0 ml sample of serum and plasma served as controls. Observations for cloudiness, precipitation, or coagulation were made at room temperature hourly for 6 hours. All samples were refrigerated overnight, then returned to room temperature and again observed for compatibility evaluation at 24 hours.
RESULTS & CONCLUSIONS
The 1:1 dilution of serum and azithromycin showed slight hemolysis at the 24 hour observation period. All other dilutions of the human serum and plasma showed no hemolysis. The dilutions for compatibility evaluation showed no cloudiness, precipitation, nor coagulation over the observation period of one to 24 hours.

SUMMARY AND EVALUATION
The following intravenous toxicity studies were reviewed and summarized in the present submission:
1. Azithromycin citrate, administered i.v. to Sprague Dawley rats at 10 or 20 mg/kg/day for 14 consecutive days, and 20 mg/kg every other day for 7 doses, produced no adverse effects on food consumption, body weight gain, appearance or behavior. Serum chemistry, hematology, and urinalysis parameters analyzed were normal. There was no evidence of elevated serum hepatic enzyme levels or of tissue phospholipidosis.

2. Azithromycin fumarate, administered i.v. to S.D. rats in doses of 5, 10 and 20 mg base/kg/day for 16-17 days, was well tolerated and had no untoward effect on body weight, food consumption, appearance or on overt behavior. Serum levels of drug showed a dose-dependent increase and were about 1.5 to 2-fold higher on day 15 as compared to day 1. There were no significant drug-related effects on clinical chemistry, hematology or urinalysis parameters. Phospholipidosis in the large intrahepatic bile duct epithelium was observed in 80% of the high-dose (20 mg/kg) animals, but did not occur in other tissues or at lower doses in this study.

3. Azithromycin administered i.v., in citrate solution, to S.D. rats in doses of 5, 10 and 20 mg/kg/day for 36-39 consecutive days, had no effect on food consumption and body weight gain. No drug-related ocular changes were observed in any rat. There were no drug-induced changes in any serum chemistry, hematology, or urinalysis parameters. Serum concentrations of azithromycin were dose-related and showed no significant changes over the course of the study. Splenic tissue concentrations in the animals at 20 mg/kg/day, was higher than hepatic tissue concentrations at all time points. The mean concentrations of azithromycin in the liver and the spleen exceeded the mean concentrations in the serum by 490 to 2400-fold, respectively. There were no drug-related alterations in liver, kidney or testis. Drug-related

phospholipidosis in the epithelium of the large bile ducts was observed in all rats treated at high-dose, however, no evidence of phospholipidosis at the 5 mg/kg/day dose level was seen.

4. Azithromycin, administered i.v., in aqueous citric acid solution, to beagle dogs at 10 or 20 mg/kg/day for 14 consecutive days and 10 mg/kg every other day for 7 doses, produced no untoward effects on food consumption, body weight gain, or on appearance or behavior. Occasional episodes of emesis and unformed stools occurred in the 10 and 20 mg/kg/day treatment groups. Mild increases in serum liver SGPT, ALP, and SGOT activity occurred at high-dose levels. There were no serum enzyme changes in those dogs receiving 10 mg/kg every other day. All other serum chemistry, hematology, and urinalysis data in all dogs were unremarkable. The plasma concentration of azithromycin on day 7, at 15 minutes following drug treatment was 2.3 µg/ml in the 10 mg/kg, every-other-day treatment group. Furthermore, the concentration of azithromycin in the plasma on day 7, at 15 minutes post-dose were 3.4, and 3.7 µg/ml in the 10 and 20 mg/kg/day dose groups, respectively. There were detectable azithromycin plasma levels in all dogs at 24 hours post-dose. Phospholipidosis was seen within the lamina propria of the gall bladder and germinal centers of the mesenteric lymph nodes of dogs receiving 20 mg/kg/day. Phospholipidosis was not observed in either the daily treatment or in the every-other-day treatment with the azithromycin, 10 mg/kg groups.

5. Azithromycin fumarate, given i.v. to beagle dogs at 0, 5, 10 or 20 mg base/kg/day for 15 consecutive days, produced no untoward effects on food consumption, body weight gain, or on appearance or behavior. No changes in serum liver enzyme activity were observed in any dog. Serum drug levels were dose-related. Electrocardiograms and blood pressures were all unremarkable at all dose levels. No treatment-related effects were detected in serum chemistry, hematology or urinalysis parameters. No effects on absolute or relative organ weights were evident, nor were there any compound-related pathologic findings. None of the treated dogs had any histological evidence of phospholipidosis. The results of the study indicated that 20 mg base/kg/day is a No-Observable-Effect Level (NOEL) for the intravenous administration of azithromycin fumarate in beagle dogs.

6. Azithromycin administered i.v. to beagle dogs in doses of 0, 5, 10 and 20 mg/kg/day for 1 month (36 days), was well tolerated. All dogs showed no remarkable changes in EKG and blood pressure values. No drug-induced ocular lesions were identified. Food consumption and weight gain were not affected. Clinical pathology data showed increases in SGPT and serum alkaline phosphatase

activities at the high dose level. There were no changes in serum enzyme activities at the 10 mg/kg/day dose level. The mean serum concentrations of azithromycin were dose-dependent. Tissue concentrations of azithromycin were higher in the spleen than in the liver, with mean spleen concentrations of 99, 525, and 1450 µg/g in the 5, 10, and 20 mg/kg/day dose group, respectively as compared to the mean liver concentrations of 45, 180, and 565, respectively. No sex-related differences were observed in azithromycin tissue concentrations. Phospholipidosis was seen at the high dose: minimal to mild in the large bile ducts of 6/6; minimal in the gall bladders of 4/6, tonsils, 2/6 and mesenteric lymph nodes, 1/6. One 10 mg/kg dog also showed minimal phospholipidosis in the large bile ducts. No evidence of phospholipidosis at 5 mg/kg/day in the dog was seen.

7. The gross and microscopic irritation potential of azithromycin in solution was investigated in the rabbits with a single 10 mg/kg dose of 1% (10 mg/kg/ml) solution of azithromycin fumarate, injected into one marginal ear vein of 6 albino rabbits and saline was used as the control in the opposing ear. The rabbits were sacrificed 24 or 48 hours after dosing. All rabbits were asymptomatic throughout test period, and there were no adverse effects on food consumption or body weight. Observed tissue change was minimal perivascular reddening at the point of injection or along the vein; changes which was attributed to the trauma of the injection. Microscopic changes reported included moderate perivascular hemorrhage, mild edema, moderate focal phlebitis and, in two cases, focal thrombosis. Therefore, azithromycin (10/kg) solution was considered to be minimally irritating to the marginal ear vein of the rabbit.

8. The hemolytic potential and compatibility of azithromycin were evaluated by the <u>in-vitro</u> method using human serum and plasma. A 1:1 dilution of the serum and azithromycin showed slight hemolysis at the 24 hour observation period. All other dilutions of the human serum and plasma showed no hemolysis. The tested serum and plasma samples in the compatibility assay showed no cloudiness, precipitation, nor coagulation over the observation period of one to 24 hours.

<u>RECOMMENDATION:</u>

I. This submission proposes to use Zithromax (Azithromycin for intravenous (i.v.) injection) for the treatment of patients with Community-Acquired Pneumonia (CAP) or Pelvic Inflammatory Disease (PID).

II. The results of the reviewed special i.v. studies in this document were consistent with those previously reported following oral administration of azithromycin in dogs and rats, which indicated that there were no unique toxicities associated with the i.v. administration of azithromycin in these species. These studies support the i.v. use of azithromycin in man. All other preclinical and safety studies referenced by the sponsor, including reproduction and genotoxicity studies of Azithromycin in the oral formulation, were submitted and previously reviewed in connection with the approved NDA 50-670.

III. I have no objections to the approval of this application [NDA 50-733 (000)] from the standpoint of pharmacology and toxicology.

Oluwadare M. Adeyemo 6/20/96
Oluwadare M. Adeyemo, Ph.D.
Pharmacologist, HFD-520

cc: NDA 50-733 (000)
HFD-340
HFD-520/Pharm/MAdeyemo
HFD-520/MO/~~JSoreth~~/MOLEDINA/ALLEVENE
HFD-520/Chem/JTimper
HFD-520/CSO/JCintron
HFD-520/Micro/HSilver
HFD-520/Biopharm/HSun
HFD-520/Statist/DLin

Concurrence Only:
HFD-520/Dep.DD/LGavrilovich
HFD-520/Team-Leader/REOsterberg
REO 6/24/96

7/5/96

Attachments: Pharmacological and Toxicological preclinical and safety studies referenced in this submission, including reproduction and genotoxicity studies of Azithromycin in the oral formulation, which were previously reviewed in connection with approved NDA 50-670.

Key words: Zithromax, Azithromycin, Macrolide, Community acquired pneumonia, Phospholipidosis, Hepatoxicity, Granulomatous inflammation, and Perivacular hemorrhage.

Consult #596 (HFD-520)

ZITHROMAX azithromycin for intravenous injection

ZITHROMAX is the trademark for an already approved and marketed preparation. The LNC found no look alike/sound alike conflicts nor misleading aspects in the the proprietary name.

The Committee believes the correct established name for the product should be azithromycin for injection to be in conformance with the USP parenteral categories.

The LNC has no reason to find the proposed proprietary name unacceptable.

D Boring 5/23/96, Chair
CDER Labeling and Nomenclature Committee

(596)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: DAN Boring, Ph.D.

FROM: Division of Anti-Infectives HFD- 520
Attention: JIM TIMPER Phone 827-2193

DATE: 4/10/96

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Zithromax NDA/ANDA# 50-733

Company Name: Pfizer, Inc.

Established name, including dosage form: Lyophilized powder
Zithromax (Azithromycin for intravenous injection), 100 mg/mL

Other trademarks by the same firm for companion products:
Zithromax : suspension, tablets, capsules

Indications for Use (may be a summary if proposed statement is lengthy):
Community-Acquired Pneumonia
Pelvic Inflammatory Disease

Initial comments from the submitter: (concerns, observations, etc.)

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Clinton
520
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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-733 CHEM.REVIEW #: 1 REVIEW DATE: 3/29/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	2-5-96	2-6-96	4-11-96

NAME & ADDRESS OF APPLICANT:

Pfizer Inc.
Regulatory Affairs Division
235 East 42nd Street
New York, NY 10017-5755
212-573-3412; FAX 212-573-1563

CONTACT:
Robert B. Clark

DRUG PRODUCT NAME

Proprietary: Zithromax
Established: Azithromycin Dihydrate
Code #: CP-62,993

PHARMACOLOGICAL CATEGORY/INDICATION:
Azalide Antibiotic
DOSAGE FORM: Intravenous injection
STRENGTHS: 100 mg/mL
ROUTE OF ADMINISTRATION: Injection
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Azithromycin USP, $C_{38}H_{72}N_2O_{12}$; 729.00

(1) 1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]-, [2R*-(2R*,3S*,4R*,5R*,8R*,10R*,11R*,12R*, 13S*, 14R*)]-;

(2) (2R,3S,4R,5R,8R,10R,11R,12R, 13S, 14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one;

(3) 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

CAS-83905-01-5; CAS-117772-70-0 [dihydrate].

SUPPORTING DOCUMENTS:

NDA 50-670; DMF DMF DMF IND
IND IND

RELATED DOCUMENTS:

NDA 50-710; NDA 50-711; NDA 50-693; NDA 50-730.

CONSULTS:

- 4/9/96: A review of considerations for environmental assessment was prepared by this reviewer and submitted for concurrence to Nancy Sager, Environmental Scientist, CDER. This review incorporates comments from that initial review to the firm needed to complete that review.

- 4/9/96: A consult was prepared and submitted for sterility CMC review to P. Cooney, HFD-160.

- 4/10/96: A method validation package was prepared and submitted to Ella Walker (718-965-5033), New York Regional Laboratory, 850 3rd Ave., Brooklyn, NY 11232-1593.

- 4/10/96: A consult was prepared and submitted for suitability of the trade name in the labeling to the Labeling and Nomenclature Committee.

- An establishment evaluation request was submitted at the time of this review; The EER number is 9968.

REMARKS/COMMENTS:

A New Drug Application for azithromycin dihydrate drug substance and 250 mg azithromycin capsules (NDA-50-670) was submitted on April 11,1990. The NDA was amended with additional information throughout the review period and the NDA, as amended, was approved by the Agency on November 1, 1991 for the treatment of lower and upper respiratory infections, skin and skin structure infections, and sexually transmitted diseases. A summary of the chemistry, manufacturing and controls for the drug substance, azithromycin dihydrate. was presented in the Summary, Section II, of approved NDA-50-670 and is incorporated in this NDA by reference. The final step in the azithromycin dihydrate synthesis is a recrystallization to the dihydrate form of azithromycin. Additional precautions to control endotoxins are employed during the final step when manufacturing drug substance for the injectable formulation. These precautions include manufacturing

under endotoxin-controlled conditions and using purified process water (low endotoxin).

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable with regard to chemistry, manufacturing, and controls. The following consults are incomplete at this time:

- 4/9/96: A review of considerations for environmental assessment was prepared by this reviewer and submitted for concurrence at the time of this review to Nancy Sager, Environmental Scientist, CDER. There are comments to the firm with this review based on comments from Nancy Sager.

- 4/9/96: A consult was prepared and submitted for sterility CMC review to P. Cooney, HFD-160.

- 4/10/96: A method validation package was prepared and submitted to Ella Walker (718-965-5033), New York Regional Laboratory, 850 3rd Ave., Brooklyn, NY 11232-1593.

- 4/10/96: A consult was prepared and submitted for suitability of the trade name in the labeling to the Labeling and Nomenclature Committee.

- An establishment evaluation request was submitted on 4/11/96; The EER number is 9968.

JT-h 4/11/96

J. Timper, Review Chemist

cc: Org. NDA 50-733
HFD-520/Division File
HFD-520/SBRoy/Teamleader JT 5/9/96
HFD-520/Timper/CHEM 4/11/96
HFD-520/Bais/MO
HFD-520/Adeyemo/Pharm
HFD-520/Silver/MICRO
HFD-520/Cintron/CSO
HFC-130/JAllen

Food and Drug Administration

[Docket No. 92N-0146]

Environmental Assessments and Findings of No Significant Impact

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it has received environmental assessments (EA's) and issued findings of no significant impact (FONSI's) relating to the approval of new drug applications (NDA's) for the following products: Cefzil (cefprozil) tablets and powder; Lorabid (loracarbef) powder and capsules; Mazicon (flumazenil) injection; Mivacron (mivacurium chloride) injection and infusion; and Zithromax (azithromycin) capsules. FDA is publishing this notice under section 102 of the National Environmental Policy Act (42 U.S.C. 4332), 21 CFR 25.41(b), and 40 CFR 1506.6.

ADDRESSES: The EA's and FONSI's may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8049.

SUPPLEMENTARY INFORMATION: The National Environmental Policy Act (NEPA) requires all Federal agencies to "use all practicable means and measures, including financial and technical assistance, in a manner calculated to foster and promote the general welfare, to create and maintain conditions under which man and nature can exist in productive harmony, and fulfill the social, economic, and other requirements of present and future generations of Americans." (See 42 U.S.C. 4331(a).) Under NEPA, all Federal agencies must prepare detailed statements assessing the possible environmental impact of, and alternatives to, major Federal actions significantly affecting the environment, and such statements are to be made available to the public. (See 42 U.S.C. 4332, 21 CFR 25.41(b), and 40 CFR 1506.6.)

FDA implements NEPA through its regulations at 21 CFR part 25. Under those regulations, the approval of an NDA usually constitutes an action that ordinarily requires the preparation of an EA. (See 21 CFR 25.22(a)(14).)

FDA recently approved NDA's pertaining to the following products: Cefzil (cefprozil), NDA 50-664 (tablet) and NDA 50-665 (powder); Lorabid (loracarbef), NDA 50-667 (powder) and NDA 50-668 (capsule); Mazicon (flumazenil), NDA 20-073; Mivacron (mivacurium chloride), NDA 20-096; and Zithromax (azithromycin), NDA 50-670.

The agency has reviewed the EA's submitted for each NDA and has prepared a FONSI for each. No environmental impact statements, therefore, are necessary. This notice announces that the EA's and FONSI's for these human drug products may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: June 12, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 92-14429 Filed 6-18-92; 8:45 am]

BILLING CODE 4160-01-F

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiological #1

NDA #50-733 **DATE COMPLETED: 1/26/97**

APPLICANT:
Pfizer Inc.
235 East 42nd Street
New York, New York 10017-1563

CONTACT PERSON(s):
Margaret A. Longshore, Ph.D. and/or Robert B. Clark
Director, Regulatory Affairs Regulatory Affairs
Tel: (212)--573-2556 Tel: (212)--573-3412

SUBMISSION REVIEWED:
PROVIDING FOR:
ZITHROMAX® (azithromycin for intravenous injection) for the treatment of patients with community-acquired pneumonia (CAP) or pelvic inflammatory disease (PID) who require initial intravenous antibiotic therapy.

PRODUCT NAMES(S):

Proprietary:	ZITHROMAX®
Non-Proprietary/USAN:	azithromycin
Code Name:	DL-8280; HOE 280
CAS No.:	*CAS-83905-01-5;* *CAS-117772-70-0* (dihydrate)

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.:

Azithromycin:

Chemical Name	=	See 1996 USAN (Page 71)
Molecular Formula	=	$C_{38}H_{72}N_2O_{12}$
Molecular Weight	=	749.00

DOSAGE FORM: Injection:: 10 mL vial containing 500 mg azithromycin (as lyophilized powder to be reconstituted).

ROUTE OF ADMINISTRATION: Intravenous (IV)
STRENGTH: 100 mg/mL (as reconstituted solution)

PHARMACOLOGICAL CATEGORY:
Antibiotic Drug (Macrolide)

DISPENSED: ___x___ **Rx** _____ **OTC**

INITIAL SUBMISSION: 2/05/96
Received by CDER: 2/06/96
Received by HFD-520: 2/08/96
Assigned to Reviewer: 2/22/96

AMENDMENT(S): N/A
PATENT:N/A

RELATED DOCUMENTS:
DMF. DMF
and DMF
IND IND and IND

NDA 50-670, ZITHROMAX (azithromycin capsules), approved for use in the treatment of respiratory tract infections, skin and skin structure infections, and *Chlamydia trachomatis* genitourinary infections in patients 16 years of age or older, on 11/01/91.

NDA 50-693, provided for a single 1-gram dose packet, approved on 9/28/94.

NDA 50-710, ZITHROMAX (azithromycin for oral suspension), approved for the treatment of acute otitis media and streptococcal pharyngitis/tonsillitis in pediatric patients, on 10/19/95.

CONSULTS: None

COMMENTS:

This drug is the subject of the compendial monographs, 21 CFR §452.60 (azithromycin), 21 CFR §452.160a (azithromycin capsules, 21 CFR §452.160b (azithromycin for oral suspension) and 23 USP (Azithromycin) on pages 152 & 153, and 23 USP (Azithromycin Capsules) on page 153, respectively.

CONCLUSIONS:

From the microbiological perspective, Pfizer should be notified that NDA 50-733 is "approvable". (See the PACKAGE INSERT section at the end of this Review, on pages 33 to 40, respectively.)

TABLE OF CONTENTS

INTRODUCTION

In 1993, it was recommended by the American Thoracic Society for therapy and treatment of hospitalized patients with community-acquired pneumoniae (CAP) to use a beta-lactam drug with or without addition of a macrolide for ~ 7 to 10 days. However, > 10 days when an atypical infection is suspected or proven. The recommendation for a combination of drug classes was necessary so that the regimen provides cover on the atypical pneumonia pathogens, which are not susceptible *in vivo* to beta-lactam drugs, and on microorganisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, respectively.

Azithromycin's spectrum of activity encompasses all the pathogens in CAP. This includes *Haemophilus influenzae*. However, erythromycin's (also a macrolide) spectrum of activity is only borderline against *H. influenzae* and the atypical bacteria. Azithromycin's pharmacokinetic profile includes lung and alveolar macrophage penetration properties and allows for once daily dosing throughout the course of therapy and treatment.

There are patients with either community-acquired pneumonia (CAP) or pelvic inflammatory disease (PID) who require hospitalization and initial intravenous therapy, for example antibiotic therapy (such as the proposed ZITHROMAX® (azithromycin for intravenous injection -- lyophilized powder). These patients are more severely ill or cannot tolerate initial oral therapy. In the initial hospitalization, it is common medical practice to initiate antibiotic therapy for these patients and when their condition warrants and later replace IV medication with an oral agent.

Therefore, the applicant is requesting their drug product be used in the treatment of community-acquired pneumoniae (CAP) due to the following microorganisms: *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Support for the use of the drug product in the treatment of CAP is generated from 5-clinical trials. The 5-clinical trials consisted of 2-USA clinical and microbiologic studies: Protocols #93CE33-0618 & #93CE33-0625, and 3-non USA efficacy and safety profile studies: Protocols #066-349, #066-350, & #066-359, respectively.

The applicant is also requesting their drug product be used in the treatment pelvic inflammatory disease (PID) due to the following microorganisms: *Bacteroides bivius, Chlamydia trachomatis,* Mycoplasma *hominis, Neisseria gonorrhoeae, Peptostreptococcus* species (spp.) *Streptococcus agalactiae* or *Ureaplasma urealyticum* in patients who also require initial intravenous therapy.

The female population who require initial hospitalization are frequently discharged after 1 to 2-days of inpatient treatment. In 1993, CDC recommended for the treatment of pelvic inflammatory disease (PID) intravenous cefoxitin or cefotetan with oral doxycycline; a beta-lactam drug to be given for at least 48 hours after demonstration of clinical improvement for 14 days. The recommended combination regimen covers the aerobic, anaerobic, and other pathogens (e.g., *Mycoplasma, Ureaplasma,* and *Chlamydia* species).

Azithromycin's microbiological and pharmacokinetic properties make possible monotherapy for PID which begins as inpatient treatment with one or two doses by the I.V. route and then continues with oral administration at a lower dose after discharge from the hospital. Pharmacokinetic studies in animals and humans suggest that sufficient therapeutic concentrations of azithromycin would be maintained in body tissues to allow an oral follow-on regimen of much shorter duration (up to 7 days) than the current 14 days recommended for doxycycline.

Support for the use of the drug product in the treatment of PID is generated from 2-clinical trials (non-USA). The 2-clinical trials consisted of 1-clinical and microbiologic study (Protocol #066-341) and 1-efficacy and safety study (Protocol #066-342), respectively.

PRECLINICAL EFFICACY (In Vitro)

MECHANISM OF ACTION

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and exerts its antimicrobial effect by interference with bacterial protein synthesis. The macrolide antibacterial agent, azithromycin, is able to concentrate in phagocytes (possibly due to its amphiphilic properties), which enables the drug to be delivered to infection sites, and thus is effective in the treatment in CAP and PID, including infections due to intracellular pathogens. For additional information, refer to the original submission, NDA 50-670, Vol. 7, Microbiology Section, Item 7.III., on pages 17 to 19, and approved on 11/01/91.

Antimicrobial Spectrum of Activity

Much of the information can be found in the original submission, NDA 50-670, Vol. 1.27, Microbiology Section, Item 7.III., on pages 21 to 109, and approved on 11/01/91. [Also refer to NDA 50-710, ZITHROMAX (azithromycin for oral suspension), approved for the treatment of acute otitis media and streptococcal pharyngitis/tonsillitis in pediatric patients, on 10/19/95.] However, some additional non-clinical *in vitro* published studies with relevant information on various microorganisms not recommended in the initially intended separate Package Insert for the intravenous drug product on the first listing (List #1) of microorganisms, but supportive on the requested second listing ("*In Vitro Only*") of microorganisms, are, as follows:

Barry and Fuchs (1) performed broth dilution tests using randomly selected 2,671 respiratory tract isolates from 19 medical centers throughout the continental USA (as part of a 1992 and 1993 surveillance program). The *in vitro* tests compared 5-study drugs: azithromycin, a streptogramin (RP59500), erythromycin, dirithromycin, and clarithromycin against the microorganisms *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, respectively. Azithromycin (an azalide) and the other 3-macrolides have similar mechanisms of action, and thus showed nearly complete cross-susceptibility and cross-resistance. The broth microdilution

tests were almost in accordance with the methods of the National Committee for Clinical Laboratory Standards (NCCLS, Approved Standard, M7-A3, 1993). Haemophilus Test Medium (HTM) was used to test all 4-isolates. The investigators indicate that, except for *Haemophilus influenzae*, MICs of macrolides are the same or 1-doubling concentration greater than those if tested in 3 to 5% lysed horse blood (LHB). β-Lactamase testing (*Haemophilus* influenzae and Moraxella catarrhalis) and penicillin (1-μg oxacillin disk screening test) susceptibility (Streptococcus pneumoniae) were performed. TABLE 1 summarizes the results of azithromycin against *Streptococcus pyogenes* in this study.

TABLE 1*

Relative Potency of Azithromycin against S. pyogenes

Microorganism (No. of Isolates)	Antimicrobial Agent	MIC (μg/mL) Range	MIC_{50}	MIC_{90}
Streptococcus pyogenes (641)	Azithromycin	≤0.25->32	≤0.25	0.5

* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Page 7-173.

The results demonstrated that azithromycin is very active against the *Streptococcus pyogenes* isolates (MIC_{90} = 0.5 MIC μg/mL).

Streptococcus pyogenes isolates were also separated into 1 of 3-subgroups according to erythromycin resistance (Erythromycin Susceptible = MIC ≤ 0.5 μg/mL; = Erythromycin Intermediate = MIC = 1.0 or 2.0 μg/mL; and Erythromycin Resistant = MIC ≥ 4.0 μg/mL). The number of isolates for each interpretative category on *Streptococcus pyogenes* were as follows: Erythromycin Susceptible = 618; Erythromycin Intermediate = 8; and Erythromycin Resistant = 15 (= 2%). TABLE 2 summarizes also the results on *Streptococcus pyogenes* in this study.

TABLE 2*

In Vitro Activity of Azithromycin against Respiratory Isolates: Susceptible, Intermediately Resistant, or Resistant to Erythromycin

Antimicrobial Agent	*Streptococcuss pyogenes* MIC (μg/mL) MIC_{50}	MIC_{90}
Azithromycin		
S[a]	≤ 0.25	≤ 0.25
I[b]	8	-[d]
R[c]	8	32

* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Page 7-174.

a. S =Susceptiblee
b. I = Intermediate
c. R = Resistant
d. - = The MIC_{90} for 90% of the strains was not calculated for groups of fewer than 10 strains.

The summary results demonstrated that azithromycin is very active against the *S. pyogenes* erythromycin-susceptible isolates (both the MIC_{50} and MIC_{90} ≤ 0.25 μg/mL).

Bauernfeind (2) analyzed the antibacterial activities of recently developed and established macrolides. A total of 920 recent clinical isolates from 83 species were investigated. The isolates were isolates were cultured from various sources, for example, from specimens of blood, sputum, feces, urine, swabs of wound sites, ears, noses, and throats. The study drugs included 14-membered macrolides, such as: erythromycin, clarithromycin, dirithromycin, and roxithromycin; 15-membered macrolide containing nitrogen, such as, azithromycin: and a 16-membered macrolide, such as: josamycin. MICs were determined as follows: Method: Agar dilution technique; Inoculum: 10^4 CFU per spot (10^5 CFU per spot for anaerobes); Used a multipoint inoculator to a series of agar plates which contained antibiotic in 2-fold dilutions; Incubation: 16 hours (24 hours for

methicillin-resistant staphylococci and 48 for anaerobes, *Bordetella pertussis* and *Helicobacter pylori*) at 35°C. MIC was determined as the lowest concentration of antibiotic at which no visible growth or growth of 3 colonies or less was observed. Mueller-Hinton agar (Difco) was the standard medium. The medium was supplemented by 7% sheep blood for hemolytic streptococci, *Streptococcus milleri*, *Streptococcus mitior*, *Streptococcus pneumoniae* and *Listeria* species. For *Haemophilus* species, *Neisseria gonorrhoeae* and *Bordetella pertussis* peptone agar (Difco) was supplemented with 8% human erythrocytes and 2% horse serum; the agar plates were incubated in a candle jar. For anaerobes, Wilkins-Chalgren Agar (Oxoid) supplemented with 10% sheep blood was used. *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* ATCC 29213 were used as MIC reference strains. TABLE 3 summarizes the results of one of the study drugs (azithromycin) against various selected microorganisms in

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* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Page 7-174.

a. S =Susceptiblee
b. I = Intermediate
c. R = Resistant
d. - = The MIC_{90} for 90% of the strains was not calculated for groups of fewer than 10 strains.

The summary results demonstrated that azithromycin is very active against the *S. pyogenes* erythromycin-susceptible isolates (both the MIC_{50} and $MIC_{90} \leq 0.25$ $\mu g/mL$).

Bauernfeind (2) analyzed the antibacterial activities of recently developed and established macrolides. A total of 920 recent clinical isolates from 83 species were investigated. The isolates were isolates were cultured from various sources, for example, from specimens of blood, sputum, feces, urine, swabs of wound sites, ears, noses, and throats. The study drugs included 14-membered macrolides, such as: erythromycin, clarithromycin, dirithromycin, and roxithromycin; 15-membered macrolide containing nitrogen, such as, azithromycin: and a 16-membered macrolide, such as: josamycin. MICs were determined as follows: Method: Agar dilution technique; Inoculum: 10^4 CFU per spot (10^5 CFU per spot for anaerobes); Used a multipoint inoculator to a series of agar plates which contained antibiotic in 2-fold dilutions; Incubation: 16 hours (24 hours for

TABLE 3*

In Vitro Activity (mg/L) of Azithromycin against Various Selected Study Microorganisms

Microorganism (No.)	Compound	MIC (mg/L) Range	MIC_{50}	MIC_{90}
Group A streptococci (22)	Azithromycin		0.06	0.13
Group B streptococci (38)	Azithromycin		0.06	0.13
Group C streptococci (21)	Azithromycin		0.13	0.13
Group G streptococci (25)	Azithromycin		0.13	0.13
Bordetella pertussis (7)	Azithromycin		0.016	0.06
Haemophilus parainfluenzae (10)	Azithromycin		0.5	2
Peptostreptococcus prevotti (2)	Azithromycin		-	-
Bacteroides spp.** (11)	Azithromycin		1	2

* Adapted from NDA 50-733, Vol. 24/137, TABLE, located on Pages 7-184 to 7-189.

** Includes: *Bacteroides bivius* [now called *Prevotella bivia*](1), *B. fragilis* (3), *B. thetaiotaomicron* (2), *B. vulgatus* (2), *B. ovatus* (1), and B. disiens (1).

The results demonstrated that azithromycin is very active against the Group A,B,C,G streptococci (MIC_{90} = 0.13 mg/L) and the *Bordetella pertussis* isolates (MIC_{90} = 0.06 mg/L). Incomplete results on *Peptostreptococcus prevotii* to make any definitive comments. The *Bacteroides* species [which contained only 1-*Bacteroides bivius* (now call *Prevotella bivia*) isolate] resulted in a MIC_{90} = 2 mg/L. Some of the other *Bacteroides* species may have caused a higher MIC_{90} value in the study.

In another study, Fass (3), the MICs of the study drugs: Bay y 3118, azithromycin, ciprofloxacin, ofloxacin, clarithromycin, cefuroxime, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole (TMP/SMZ) for 878 recent clinical isolates were determined using broth microdilution methods. The bacterial strains were arbitrarily selected from isolates at the Ohio State College Hospitals. They were fresh isolates collected during November 1992 through January 1993. Duplicate isolates from the same patients were excluded. Laboratory standard powders were diluted and dispensed into microdilution plates by using an MIC-2000 dispensing machine in log dilution steps from μg/mL, (except for TMP/SMZ). Plates were stored at -70°C until used. MICs were determined by a standardized microdilution method (NCCLS, M7-A2, 1990) using cation-adjusted Mueller-Hinton broth and *Haemophilus* Test Medium (HTM) for the non-fastidious microorganisms and Haemophilus influenzae, respectively. HTM was also used for Streptococcus pyogenes, Streptococcus pneumoniae, and the viridans group streptococci. Incubation was in room air for ~ 20 hours. For anaerobes, the investigator used Schaedler broth (Difco) supplemented with 1% heat-activated horse serum and 0.5 μg of vitamin K_1 per mL. Incubation was in 85% N_2-10% H_2-5% CO_2 for ~ 48 hours. Final inoculum was ~ 5×10^5 CFU/mL. NCCLS recommended control strains (NDA 50-733, Vol. 24/137, on Page 2356) were used. In addition, The investigator used scattergrams and regression analyses to compare *in vitro* activities and describe cross-susceptibility and cross-resistance among the principal test drugs (quinolones). TABLE 4 summarizes the results of azithromycin against various selected microorganisms in this study.

TABLE 4*

In Vitro Activity (μg/mL) of Azithromycin against Various Selected Study Microorganisms

Microorganism (No.)	Drug	MIC (μg/mL) Range	MIC_{50}	MIC_{90}
Streptococcus pyogenes (20)	Azithromycin		0.25	0.25
Streptococcus agalactiae (24)	Azithromycin		0.25	0.25
Viridans Group streptococci (17)	Azithromycin		0.025	4
Peptostreptococcus species (30)	Azithromycin		1	4

* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Pages 7-268 to 7-272.

The MIC_{90s} demonstrated that azithromycin is very active against Streptococcus pyogenes (MIC_{90} = 0.25 μg/mL) and Streptococcus agalactiae (MIC_{90} = 0.25 μg/mL) and less active against the Viridans group streptococci (MIC_{90} = 4 μg/mL) and Peptostreptococcus study isolates (MIC_{90} = 4 μg/mL), respectively.

Felmingham et al. (4) studied the activity of azithromycin, erythromycin, clarithromycin, roxithromycin, midecamycin acetate, amoxicillin, amoxicillin plus clavulanic acid (2mg/L) and flucloxacillin against clinical isolates found in infections of the upper and lower respiratory tract, skin and soft tissue, genital tract and gastro-intestinal tract. The latter isolates include: *Streptococcus* spp., *Mycoplasma pneumoniae, Legionella* spp., *Ureaplasma urealyticum, Campylobacter jejuni, Chlamydia trachomatis,* and others. The majority of the *Ureaplasma urealyticum, Staphylococcus* spp., and *Mycoplasma hominis* bacterial isolates were from clinical material examined in the Department of Clinical Microbiology, University College Hospital, London. Others clinical isolates were provided by other hospitals in the United Kingdom and overseas. *Staphylococcus aureus* (NCTC 6571) was used as the quality control strain. Mueller-Hinton agar medium (Oxoid) containing saponin-lysed horse blood (5% v/s) was used for the MIC determination(s) on *Staphylococcus* species. The inoculum used was ~ 10^4 CFU/mL. Incubation overnight was at 35°C. Supplemented and buffered yeast extract agar, pH 6.9 (Oxoid), containing water-lysed horse blood (10% v/v) was used for the MIC determination(s) on *Legionella* species. The inoculum used was ~ 10^4 CFU/mL. Incubation was for 48 hrs. at 37°C. *Mycoplasma* microbroth medium containing gamma-globulin free horse serum (20% v/v) and supplemented with glucose (0.1% w/v, pH 7.6), arginine (0.1% w/v, pH 7.0), urea (0.1% w/v, pH 6.5) was used for the MIC determination(s) *Mycoplasma pneumoniae, Mycoplasma hominis* and *Ureaplasma urealyticum*. The inoculum used was ~ 10^5 CFU/mL. Incubation was for 48 hrs. at 37°C. TABLE 5 and TABLE 6 summarizes the results of azithromycin against various selected microorganisms in this study.

TABLE 5*

In Vitro Activity (μg/mL) of Azithromycin against *Staphylococcus* isolates

Microorganism (No.)	Drug	MIC (μg/mL) MIC_{50} (%)	MIC (μg/mL) MIC_{90} (%)
Staphylococcus aureus [methicillin-susceptible] (50)	Azithromycin	0.25 (44/50 = 88%)	> 64 (100%)
Staphylococcus aureus [methicillin-resistant] (50)	Azithromycin	0.25 (10/50 = 20%)	> 64 (100%)
Staphylococcus species [coagulase-negative/ methicillin-susceptible] (50)	Azithromycin	0.25 (41/50 = 82%)	32 (90%)
Staphylococcus species [coagulase-negative/ methicillin-resistant] (50)	Azithromycin	0.12/32 (44%/58%)	> 64 (100%)
Staphylococcus aureus (NCTC 6571) (1)	Azithromycin	--	0.25 (100%)

* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Pages 7-280.

The MICs demonstrated that azithromycin is very active at $MIC_{80's}$ = 0.25 μg/mL of the methicillin-susceptible isolates on both the *Staphylococcus aureus* (88%) and the coagulase-negative *Staphylococcus* species (82%), respectively. For these same isolates $MIC_{90} \geq 32$ μg/mL. Azithromycin demonstrates less activity against the methicillin-resistant Staphylococcus aureus isolates.

TABLE 6*

In Vitro Activity (mg/L) of Azithromycin against *Ureaplasma urealyticum*

Microorganism (No.)	Drug	MIC (mg/L) MIC_{50}	MIC_{90}	Range (mg/l)
Ureaplasma urealyticum (20)	Azithromycin	0.25	1	0.12-1

* Adapted from NDA 50-733, Vol. 24/137, TABLE 1, on Pages 7-283.

The MIC results demonstrated that azithromycin was highly active against the 20 *Ureaplasma urealyticum* isolates.

The applicant provided non-clinical *in vitro* published studies with information on various microorganisms. Since the drug product package insert will include labeling on both the intravenous and the oral dosage forms, and also that the applicant is not recommending any new microorganisms (which are not pertinent to one or both dosage forms), the continuation on the discussion of the remaining published articles (*in vitro* activity) is stopped at this time.

MECHANISM(S) OF RESISTANCE STUDIES

No new separate studies on mechanism(s) of resistance provided in this application.

PRECLINICAL EFFICACY (*In Vivo*)

PHARMACOKINETICS/BIOAVAILABILITY

The applicant provided information on the pharmacokinetics on the drug product. It is provided in Item 6 in this application. The following is a summary as found in the most recent revised package insert on the intravenous drug product and dated 1/13/97 (Note: Information on the oral dosage will not be repeated. Refer to NDA 50-710/S-001, Package Insert labeling on the oral dosage forms and approved on 12/20/96.):

Patients hospitalized with community-acquired pneumonia (CAP) who received daily 1-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL achieved a mean maximum concentration (Cmax) = 3.63 μg/mL, 24-hour trough level = 0.2 μg/mL; and AUC24 = 9.6 μg.h/mL. In normal volunteers who received a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL the mean Cmax = 1.14 μg/mL, 24-hour trough = 0.18 μg/mL, and the AUC24 = 8.0 μg.h/mL, respectively. In addition, similar pharmacokinetic values were obtained in patients hospitalized with CAP that received the same 3-hour dosage regimen for 2 to 5 days. TABLE 7 summarizes the results.

TABLE 7

Plasma Concentrations (μg/mL) after Daily Intravenous Infusions of 500 mg Azithromycin

Infusion Concentration Duration	Time after Starting the Infusion (hr.)
2 mg/ml, 1 hr[a]	
1 mg/mL, 3 hr[b]	

a = 500 mg (2 mg/mL) for 2 to 5 days in CAP patients.
b = 500 mg (1 mg/mL) for 5 days in healthy subjects.

A comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin, shows only 8% increase in Cmax but a 61% increase in AUC reflecting the 3-fold rise in C24 trough levels.

The recommended dosage regimen for adult patients consists of a single daily IV infusion for 1 to 5 days, followed by oral therapy with ZITHROMAX®. One should also look and refer to the **INDICATIONS AND USAGE** section.

In one multiple dose study in normal volunteers and administrating a 500 mg (1 mg/mL) 1-hour intravenous dosage regimen, the administered azithromycin dose amount excreted in the urine in 24 hours ~ 11% after the 1st dose and 14% after the 5th dose. This value is greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin.

The serum protein binding of azithromycin is variable in the concentration range approximately human exposure decreasing from 51% at 0.2 μg/mL to 7% at 2 μg/mL.

The pharmacokinetic data demonstrates that azithromycin by the intravenous route provides higher initial blood levels than are achieved by the oral route, and with follow-up oral therapy, the drug is effective in the treatment of CAP and PID.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

The majority of the information is found in the original submission, NDA 50-670, Vol. 1.27, Microbiology Section, Item 7.III., on pages 57 to 78, and approved on 11/01/91. Additional relevant animal protection published studies are listed in NDA 50-333, Section 7.9. Copies of the publications are provided in Section 7.11.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

The techniques and the criteria for susceptibility testing and the interpretation of the susceptibility test results were according to the NCCLS guidelines at that time.

Isolates/Relevance to Approved Indications

The applicant recommended intravenous azithromycin (followed by oral therapy) in the treatment of Community-Acquired Pneumoniae (CAP) due to the following organisms:

Chlamydia pneumoniae
Haemophilus influenzae
Legionella pneumophila
Moraxella catarrhalis
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae

These proposed microorganisms were deemed relevant (with provided acceptable supporting clinical data) in causing the requested CAP indication, and therefore the CAP claim and all the proposed microorganisms were approved by the Medical Officer.

The applicant also recommended intravenous azithromycin (followed by oral therapy) in the treatment Pelvic Inflammatory Disease (PID) due to the following organisms:

Prevotella bivia (formerly *Bacteroides bivius*)
Chlamydia trachomatis
Mycoplasma hominis
Neisseria gonorrhoeae
Peptostreptococcus species
Streptococcus agalactiae
Ureaplasma urealyticum

The following proposed microorganisms, *Chlamydia trachomatis*, *Mycoplasma hominis*, and *Neisseria gonorrhoeae*, were deemed relevant (with provided acceptable supporting clinical data) in causing the PID indication, and therefore the PIP claim and the 3 microorganisms were approved by the Medical Officer.

The following lacked acceptable clinical data, however are relevant (*in vitro*) in possibly causing either respiratory or gynecological infections (See recommended Package Insert labeling at the end of this review).

Prevotella bivia (formerly *Bacteroides bivius*)
Peptostreptococcus species
Streptococcus agalactiae
Ureaplasma urealyticum

MIC Broth/Agar Dilution Comparisons

No new information provided. However, for the Community Acquired Pneumonia studies, the disk diffusion and the microbroth dilution procedures, including those procedures for culture and susceptibility testing on *Legionella* and *Mycoplasma* isolates, used by the applicant's reference laboratories are discussed in NDA 50-733, Vol. 1, on pages 2-69 to 2-77. For the Pelvic Inflammatory Disease studies, those procedures for specimen, collection, culture, and susceptibility testing on relevant microorganisms (*Chlamydia*, *Mycoplasma*, *Ureaplasma* species) used by the applicant's reference laboratories are discussed in NDA 50-733, Vol. 1, on pages 2-78 and 2-79.

MIC/Disk Diffusion Correlation Studies

No new information provided.

Quality Control Studies (MIC and Disk Diffusion)

No new information provided. However, the following Quality Control microorganisms were used in the susceptibility testing at the applicant's reference laboratories in the U.S. Community-Acquired Pneumonia studies.

Staphylococcus aureus	ATCC 29213
Haemophilus influenzae	ATCC 49247
Haemophilus influenzae	ATCC 49766
Streptococcus pneumoniae	ATCC 49619
Pseudomonas aeruginosa	ATCC 27853

***Haemophilus influenzae* and *Streptococcus pneumoniae* Studies**

Refer to the clinical and microbiological results on *Haemophilus influenzae* and *Streptococcus pneumoniae* under **Bacteriological Efficacy** - **Correlation of Test Results with Outcome Statistics** - **Community Acquired Pneumonia** in this Review.

BACTERIOLOGICAL EFFICACY

Correlation of Test Results with Outcome Statistics

Community-Acquired Pneumoniae (CAP)

Support for the use of azithromycin in the treatment of community-acquired pneumoniae (CAP) was generated from 5-clinical trials. The 2-pivotal clinical trials consisted of USA clinical and microbiologic studies: Protocols #93CE33-0618 & #93CE33-0625, as follows:

Clinical Study Protocol #93CE33-0618:

This study compared azithromycin in a 1:1 randomization with cefuroxime (2250 mg/day IV followed by 1000 mg/day PO), with or without erythromycin (up to 2 g/day by any route).

Clinical Study Protocol #93CE33-0625:

This clinical trial was a non-comparative study in which the primary measures of efficacy were the clinical and bacteriological outcomes by pathogen.

Discussion:

A total of 414 patients received azithromycin for their CAP in the 2-pivotal USA studies, of which ~ 25% received a 2 mg/mL azithromycin infusion over 1 hour and the others (~ 75%) received 1 mg/mL infusion over 3-hours. The applicant indicated that the predominant pathogen isolated was *Streptococcus pneumoniae*. Culture and serological evidence of infection with *Chlamydia pneumoniae* (~ 10%), *Mycoplasma pneumoniae*, and *Legionella pneumophila* (4%) were the other pathogens isolated.

The applicant used specialized diagnostic clinical laboratories for the detection and isolation, by culture and/or serology, with atypical (e.g., pneumonia) pathogens and for confirmation of susceptibilities of routine pathogens in community-acquired pneumoniae (CAP) obtained from the USA clinical studies.

USA Clinical Trials - Protocols #93-CE33-0618 and #93-CE33-0625:

The following is a summary Table (TABLE 8) on the total clinical and bacteriological outcomes on *Streptococcus pneumoniae* isolates from patients who were treated with azithromycin, in the 2-clinical trials:

TABLE 8*

Minimum Inhibitory Concentration (MIC) of Azithromycin Related to Clinical for Patients Treated with Azithromycin - *Streptococcus pneumoniae*

AZI MIC (μg/mL)	No. Isolates	Total Clinical Outcome @ 7-10 Days			Total Bacteriological Response	
		Cure	Impr.[a]	Fail[b]	Erad[c]	Pstd[d]
0.016	2	1	0	1	1	1
0.03	4	4	0	0	4	0
0.06	8	6	0	2	8	0
0.12	37	34	1	2	36	1
8	1	1	0	0	1	0
Total	52	46	1	5	50	2

* Adapted from NDA 50-733, Vol. 1/137, Table 6.2.1, on Pages 2-113 & 2-114.

a. Impr. = Improvement
b. Fail. = Failed
c. Erad. = Eradicated
d. Pstd. = Persisted

The data show the following results on the treatment using azithromycin against *Streptococcus pneumoniae*: at MIC = 0.12 μg/mL, 45/51 patients cured (88.2%) with a corresponding 49/51 (96.1%) bacteriological eradication.

The following is a summary Table (TABLE 9) on the total clinical and bacteriological outcomes on *Haemophilus influenzae* isolates from patients who were treated with azithromycin, in the 2-clinical trials:

TABLE 9*

Minimum Inhibitory Concentration (MIC) of Azithromycin Related to Clinical for Patients Treated with Azithromycin - *Haemophilus influenzae*

AZI MIC (μg/mL)	No. Isolates	Total Clinical Outcome @ 7-10 Days			Total Bacteriological Response	
		Cure	Impr.[a]	Fail[b]	Erad[c]	Pstd[d]
0.25	1	1	0	0	1	0
0.5	2	2	0	0	2	0
1	15	14	0	1	15	0
2	11	10	0	1	11	0
4	3	2	0	1	3	0
Total =	32 =	29	0	3 =	32	0

* Adapted from NDA 50-733, Vol. 1/137, Table 6.2.1, on Pages 2-115 & 2-116.

a. Impr. = Improvement
b. Fail. = Failed
c. Erad. = Eradicated
d. Pstd. = Persisted

The data show the following results on the treatment using azithromycin against *Haemophilus influenzae:* at MIC = 1.0 μg/mL, 17/18 patients cured (94.4%) with a corresponding 18/18 (100%) bacteriological eradication.

The following are separate summary Tables (TABLE 10 to TABLE 15) of the azithromycin treated patients on bacteriological outcomes of all pathogens in the 2-clinical USA trials:

TABLE 10*

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Haemophilus influenzae* isolated at Baseline in USA Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (μg/mL)	Susceptibility[d]
Haemophilus influenzae	20	1	S
	17	-	S
	25	1	S
	18	-	S
	14	1	S
	21	-	S
	19	1	S
	16	2	S
	15	1	S
	24	1	S
	16	1	S
	19	2	S
	17	-	S
	18	0.5	S
	22	0.5	S
	-	1	S
	15	2	S
	28	0.25	S
	16	2	S
	12	-	S
	21	1	S
	18	-	S
	26	-	S
	25	-	S
	25	1	S
	19	4	S
	14	1	S
	12	4	S
	26	1	S

TABLE 10* (con't)

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Haemophilus influenzae* isolated at Baseline in USA Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (μg/mL)	Susceptibility[d]
Haemophilus influenzae	23	2	S
	18	-	S
	18	1	S
	22	-	S
	16	1	S
	-	4	S
	20	2	S
	24	1	S
	24	1	S
	23	2	S
	19	2	S
	24	-	S
	15	2	S
	16	2	S
	18	2	S
	18	-	-
	17	2	S

* Adapted from NDA 50-733, Vol. 1/137, Table 10, on Pages 2-124 to 2-155.

a. Performed and obtained at a local laboratory.
b. - sign means "not done".
c. Performed and obtained at a reference laboratory.
d. S = susceptible; R = resistant or intermediate.

Comments (*Haemophilus influenzae*):

The zone diameter sizes ranged form mm. The MICs ranged from (μg/mL). All the results were interpreted as "susceptibility".

TABLE 11*

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Moraxella catarrhalis* isolated at Baseline in USA Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (μg/mL)	Susceptibility[d]
Moraxella catarrhalis	38	-	S
	23	-	S
	45	0.06	S
	23	-	S
	38	-	S
	21	0.12	S
	28	-	S
	21	0.06	S
	43	0.06	S
	25	-	S
	26	0.06	S
	33	0.06	S
	36	0.06	S
	40	0.06	S

* Adapted from NDA 50-733, Vol. 1/137, Table 10, on Pages 2-124 to 2-155.

a. Performed and obtained at a local laboratory.
b. - sign means "not done".
c. Performed and obtained at a reference laboratory.
d. S = susceptible; R = resistant or intermediate.

Comments (*Moraxella catarrhalis*):

The zone diameter sizes ranged form mm. All the MIC results were 0.06 μg/mL, except for one result (MIC = 0.12 μg/mL). All the results were interpreted as "susceptibility".

TABLE 12*

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Mycoplasma pneumoniae* isolated at Baseline in USA Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (μg/mL)	Susceptibility[d]
Mycoplasma pneumoniae	-	0.01	S
	-	0.01	S
	-	0.01	S
	-	0.01	S
	-	0.01	S

* Adapted from NDA 50-733, Vol. 1/137, Table 10, on Pages 2-124 to 2-155.

a. Performed and obtained at a local laboratory.
b. - sign means "not done".
c. Performed and obtained at a reference laboratory.
d. S = susceptible; R = resistant or intermediate.

Comments (*Mycoplasma pneumoniae*):

All the MIC results were 0.01 μg/mL. All the MIC results were interpreted as "susceptibility". There were no zone diameter results.

TABLE 13*

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Staphylococcus aureus* isolated at Baseline in USA Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (μg/mL)	Susceptibility[d]
Staphylococcus aureus	19	2	S
	24	2	S
	0	> 32	R
	30	2	S
	22	2	S
	31	-	S
	26	2	S
	24	1	S
	16	2	S
	30	2	S
	22	0.12	S
	19	2	S
	20	2	S

* Adapted from NDA 50-733, Vol. 1/137, Table 10, on Pages 2-124 to 2-155.

a. Performed and obtained at a local laboratory.
b. - sign means "not done".
c. performed and obtained at a reference laboratory.
d. S = susceptible; R = resistant or intermediate.

Comments (*Staphylococcus aureus*):

Almost all the zone diameter sizes ranged form mm. Almost all the MIC results were 2 μg/mL, except for one at 1 μg/mL and another at 0.12 μg/mL, respectively. These results were interpreted as "susceptibility". One result was interpreted as "resistant" (Zone Diameter = 0 mm; MIC = > 32 μg/mL).

TABLE 14*

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Streptococcus pneumoniae* isolated at Baseline in US Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (µg/mL)	Susceptibility[d]
Streptococcus pneumoniae	24	-	S
	25	0.06	S
	25	-	S
	25	0.12	S
	32	0.12	S
	20	-	S
	21 (Bld.)[e]	-	S
	21 (Sptm.)[f]	-	S
	-	0.12	S
	-	0.12	S
	20	-	S
	40	-	S
	30	0.03	S
	15 (I)	8 (R)	[redacted]
	33	0.12	S
	25	0.12	S
	23	< 0.016	S
	22	-	S
	23	0.12	S
	31	0.12	S
	-	0.12	S
	33	0.12	S
	39	0.06	S
	40	0.12	S
	35	0.03	S
	21	0.12	S
	20	-	S
	26	-	S
	20	0.12	S
	23	0.12	
	29	-	S
	32	0.12	S
	14	-	I
	21	0.03	S
	28	0.12	S

TABLE 14* (con't)

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Streptococcus pneumoniae* isolated at Baseline in US Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (µg/mL)	Susceptibility[d]
Streptococcus pneumoniae	30	0.12	S
	30	-	S
	-	0.12	S
	22	0.12	S
	21	-	S
	22	0.06	S
	19	0.06	S
	33	0.12	S
	31	-	S
	6	-	R
	22	< 0.016	S
	28	0.06	S
	32	-	S
	23 (Bld.)	-	S
	23 (Sptm.)	0.12	S
	-	0.12	S
	26	0.12	S
	21	-	S
	28	0.12	S
	22	0.12	S
	-	0.06	S
	24	0.06	S
	21	-	S
	21	-	S
	22	-	S
	-	0.12	S
	20	0.12	S
	23	0.12	S
	24	0.12	S
	10	-	R
	22	-	S
	22	-	S
	19	-	S
	22	-	S

TABLE 14* (con't)

Susceptibility Test Results at Local and Reference Laboratories and Final Result(s) for *Streptococcus pneumoniae* isolated at Baseline in US Studies*

Baseline Pathogen	Zone Diameter[a,b] (mm)	MIC[c] (µg/mL)	Susceptibility[d]
Streptococcus pneumoniae	23	-	S
	23	-	S
	23	-	S
	40	-	S
	22	0.12	S
	25 (Bld.)	0.12	S
	25 (Sptm.)	0.12	S
	-	0.12	S
	20 (Bld.)	0.12	S
	26 (Sptm.)	0.12	S
	20 (Bld.)	0.12	S
	21 (Sptm.)	0.12	S
	20	0.12	S
	18	0.12	S
	20 (Bld.)	0.12	S
	20 (Sptm.)	0.12	S
	22	0.06	S
	20	0.12	S
	22	0.03	S

* Adapted from NDA 50-733, Vol. 1/137, Table 10, on Pages 2-124 to 2-155.

a. Performed and obtained at a local laboratory.
b. - sign means "not done".
c. Performed and obtained at a reference laboratory.
d. S = susceptible; R = resistant; and I = intermediate.
e. Bld. = Specimen source is from blood.
f. Sptm. = Specimen source is from sputum.

Comments (Streptococcus pneumoniae:

Almost all the zone diameter sizes ranged form mm. Almost all the MIC results ranged from μg/mL (the majority results = 0.12 μg/mL). These results were interpreted as "susceptibility". There were 4 results which were interpreted as "resistant".

TABLE 15*

Azithromycin IV/PO Community - Acquired Pneumonia
USA Studies -- *Legionella pneumophila*

Baseline Pathogen	MIC (μg/mL)
Legionella pneumophila	0.14
	0.07

* Adapted from NDA 50-733, Vol. 1/137, Table 10.2, on Page 2-201.

Comments (*Legionella pneumophila*):

The 2 MIC results are very low. No zone diameter results were given.

Pelvic Inflammatory Disease (PID)

Support for the use of azithromycin in the treatment of pelvic inflammatory disease (PID) was generated from 2 clinical trials (outside the USA) The 2-pivotal clinical trials consisted of 1-clinical and microbiologic study (Protocol: #066-341) and 1-efficacy and safety (Protocol #066-342).

Clinical Study Protocols #066-341 & #066-342:

A total of 106 women received azithromycin monotherapy and 107 women received azithromycin in conjunction with metronidazole in 2-open non-USA clinical trial studies.

The 2-clinical studies (non-USA) employed 3-treatment groups: 1st group received azithromycin only (= 1-I.V. dose of 500 mg as a 1 mg/mL solution over 3-hours, followed by 250 mg/day orally for 6 days or 2 doses I.V. followed by 250 250 mg/day orally for 5-days); 2nd group received the same aforementioned course of azithromycin in conjunction with metronidazole (= given I.V. for 1- or 2-days, followed by oral dosing for a total of 12-days or solely by the oral route at 1200 mg/day for all 12-days); and a 3rd group received a comparative regimen (either doxycycline 200 mg/day for 21 days plus amoxicillin-clavulanate at 3 g/day I.V. for 5-days and 1500 mg/day PO for 16-days or a single dose of 2 g cefoxitin with probenecid on day one plus doxycycline 200 mg/day for 14-days plus metronidazole as above). The results showed that azithromycin monotherapy was as safe and effective as the combination or the comparative regimens. Also, there was no difference in efficacy was seen between groups which received 1 or 2 doses of azithromycin by the I.V. route.

Non-USA Clinical Trials - Protocols #066-341 & #066-342:

There were no summary Tables which included both the clinical and/or bacteriological outcomes (zone sizes and/or MICs) on the baseline pathogens from patients who were treated with azithromycin, in the 2 non-USA clinical trials.

PACKAGE INSERT

ISOLATES APPROVED

The following 2-indications and relevant microorganisms have been "approved" on this intravenous dosage form by the Medical Officer:

1. Community-Acquired Pneumoniae (CAP):

   Chlamydia pneumoniae
   Haemophilus influenzae
   Legionella pneumophila
   Moraxella catarrhalis
   Mycoplasma pneumoniae
   Staphylococcus aureus
   Streptococcus pneumoniae

2. Pelvic Inflammatory Disease (PID):

   Chlamydia trachomatis
   Mycoplasma hominis
   Neisseria gonorrhoeae

3. The following microorganisms: *Prevotella bivia* (formerly *Bacteroides bivius*), *Peptostreptococcus* species, *Streptococcus agalactiae*, and *Ureaplasma urealyticum* are not approved for PID on this intravenous dosage form.

INTERPRETATIVE CRITERIA ESTABLISHED

The interpretative susceptibility criteria used, as well as established, corresponds to those recommended in NDA 50-710/S-001, ZITHROMAX® (azithromycin for oral suspension), and approved on December 20, 1996. [These same interpretative susceptibility criteria are also found in the NCCLS M100-S6 Tables, dated December 1995.]

6 Pages deleted
(34-39)
Labeling Revisions

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

REFERENCES

1. Barry AL and PC Fuchs. "*In Vitro* Activities of a Streptogramin (RP59500), Three Macrolides, and an Azalide against Four Respiratory Tract Pathogens." Antimicrobial Agents and Chemotherapy. ASM.1995;**39(1)**:238-240.

2. Bauernfeind, A. "*In Vitro* Activity of Dirithromycin in Comparison with Other New and Established Macrolides." Journal of Antimicrobial Chemotherapy.1993;**31(Supp.C)**: 39-49.

3. Fass, RJ. "In Vitro Activity of Bay y 3118, a New Quinolone." Antimicrobial Agents and Chemotherapy. ASM.1993;**37(11)**:2348-2357.

4. Felmingham, D., MJ Robbins, et al. "The *In Vitro* Activity of Some 14-, 15-, and 16-Membered Macrolides Against *Staphylococcus* spp., *Legionella* spp., *Mycoplasma* spp., and *Ureaplasma urealyticum*." Drugs Exptl. Clin. Res.1991;**XVII(2)**:91-99.

Harold V. Silver (1/27/97)
Harold V. Silver
Microbiologist/DAIDP/HFD-520

cc: Orig. NDA 50-733
HFD-520/Division File
HFD-520/TLMO/MAlbuerne
HFD-520/MO/LGirardi
HFD-520/Pharm/MAdeyemo
HFD-520/Chem/JTimper
HFD-520/ProjMgr/JCintron
HFD-520/Micro/HVSilver: 1/27/97
filename(s): 50733MIC.FIN
APPROVABLE

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/TLMicro/ATSheldon
HFD-520/TLMicro/RD init. by A.T.Sheldon:
RD & Final ATS 1/27/97
1/27/97
2/5/97

APR 30 1996

Timpe
530

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 50-733
29 April 1996

A. 1. NDA 50-733

APPLICANT: Regulatory Affairs Division
Pfizer, Inc.
235 East 42nd Street
New York, New York 10017-1563

2. PRODUCT NAMES: Zithromax® (azithromycin for intravenous injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is provided in 10 mL vials containing 500 mg azithromycin for reconstitution and intravenous administration.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in the treatment of community - acquired pneumonia and pelvic inflammatory disease.

B. 1. DATE OF INITIAL SUBMISSION: 5 February 1996

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

IND	NDA 50-670	DMF
IND	NDA 50-693	DMF
IND	NDA 50-710	DMF

4. ASSIGNED FOR REVIEW: 15 April 1996

C. REMARKS: The drug product is compounded, filtered, filled, sealed, labeled and packaged at

D. CONCLUSIONS: The application is recommended for approval based on sterility assurance.

29 April 1996

Paul Stinavage, Ph.D.

FTE 4/30/96

cc: Original NDA 50-733
HFD-520/J. Timper
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 29 April 1996
R/D initialed by P. Cooney, 29 April 1996

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 50-733

ZITHROMAX
(Azithromycin Intravenous Injection, NDA 50-733)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT
NDA 50-733
ZITHROMAX
(Azithromycin Intravenous Injection)

The national Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Zithromax, Pfizer, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. Zithromax (azithromycin USP) is a macrolide systemic antibiotic. Chemically, azithromycin is 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A. The injection is 100 mg/mL. This product is a line extension of previous azithromycin dosage forms capsules and oral suspension. The FONSI for Zithromax (azithromycin) 250 mg Capsules, NDA 50-670, dated 12/17/91 is attached.

Drug substance may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The data available to the agency does not suggest that the increased use that is expected from approval of this NDA will adversely affect the environment.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Returned, rejected or out of specification goods will be disposed of by the manufacturer at a licensed incineration facility. From home use, empty or partially empty containers will

typically be disposed of by a community's solid waste management system which may include landfills incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

JTh 12/10/96

Date

Prepared by
J.Timper
Review Chemist
HFD-520

David B. Katague 12/10/96

Date

Division Concurrence
David Katague, Ph.D.
Acting Team Leader
HFD-520

12/16/96 Nancy B Sager

Date

Concurred
Nancy B. Sager
Team Leader
Environmetal Assessment Team
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

NFD-520/J. Timper for NDA 50-733 (ORIGINAL)
NFD-357/FONSI File 50733
NFD-357/Docket File
NFD-205/FOI COPY

SECTION 3.III.D. ENVIRONMENTAL ASSESSMENT

AZITHROMYCIN FOR INJECTION

NON-CONFIDENTIAL FOI SUMMARY

The applicant certifies that the Environmental Assessment (EA) provided in support of ZITHROMAX Oral, Azalide Antibiotic (NDA 50-670: approved November 1, 1991; Finding of No Significant Impact, December 17, 1991) is valid for the subject NDA for the injection dosage form; inconsequential differences/changes from the original submission are outlined below. The applicant hereby authorizes release of this Non-Confidential Summary as an FOI version (exception: Confidential Appendix relating to projected drug usage) and authorizes re-release of the FOI version, submitted 11/18/91, to the original NDA 50-670.

Specifically:

1. Format Items 4 and 6: Description of Proposed Action. Sites of Manufacture. Certification of Compliance.- Approval of the subject supplement, covering a 500 mg/vial sterile fill for reconstitution and intravenous administration, will enable use of azithromycin as an intravenous antibacterial agent, primarily in hospital settings. Manufacture of drug substance will be carried out at the sites identified in Items 4 and 6 of the original submission, and the applicant certifies that there will be no change in the production emissions regulatory compliance status of azithromycin drug substance at these sites from the addition of the subject action. Manufacture of drug product will be carried out under contract by Ben Venue Laboratories, 270 Northfield Road, Bedford, OH 44146-0568. Ben Venue Laboratories has certified that it is in compliance with all applicable emission requirements set forth in permits, consent decrees and administrative orders, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations at its Bedford facility. An Abbreviated Environmental Assessment from Ben Venue Laboratories is enclosed as Appendix 2.

2. Format Items 6, 7 and 8: Projected Usage. Fate and Effects.- The quantity of azithromycin currently projected for a mature market (ca. year 2001) has been revised, as outlined in Confidential Appendix 1. The increase over the usage projected in the original submission is judged to have no impact on the considerations about usage emissions, fate and effects outlined in Items 6, 7 and 8 of the EA in the original submission. Specifically, the safety margins to species tested (sludge respiration inhibition, microbial inhibition, daphnid acute toxicity, amphipod acute toxicity and earthworm acute toxicity) established in the original EA remain essentially unchanged.

3. Other Items Comprising EA Format 21 CFR Part 25.31a.- In addition to the specific Items discussed above -- namely, EA Items 4, 6, 7 and 8 -- the information provided in the original EA and subsequent supplements under Items 2, 3, 5, 9, 10, 11, 12, 13, 14 and 15 are judged applicable to the subject application, with the following exceptions:

   Item 5.B. Drug Product. Drug product is comprised of azithromycin dihydrate, 500 mg/vial (as azithromycin, formulated using pharmaceutically-acceptable

excipients), as a sterile fill for reconstitution to 100 mg/mL for intravenous administration.

Item 6.A.2 Controls/Compliance: See Appendix 1, enclosed, for an updated listing of regulations and permits.

4. Certification.- The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer's knowledge.

Name: Irving M. Goldman, Ph.D. Title: Director, Environmental Sciences Department, Pfizer Central Research

Irving M. Goldman
Signature

September 9, 1996
Date

enclosure:

Appendix 1.- Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments

Appendix 2.- Abbreviated Environmental Assessment. Ben Venue Laboratories, Inc.

Confidential Appendix 1.- Revised Projected Azithromycin Usage

APPENDIX 1

Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments

1. Occupational.- Workplace exposure will be in compliance with the following requirements:

    i. Groton, Barceloneta and Brooklyn facilities:
    - Permissible Exposure Limits according to 29 CFR 1910.100

    ii. Ringaskiddy facility:
    - Permissible Exposure Limits as defined by the Republic of Ireland National Health and Safety Authority

2. Atmospheric.- Emissions will be in compliance with the following requirements:

    i. Groton facility:
    - Federal Clean Air Act and Regulations
    - Connecticut General Statutes Title 22a, Chapter 446c, Air Pollution Control Laws
    - CT DEP Air Pollution Control Regulations, Title 22a, Chapter 174
    - Connecticut State Implementation Plan
    - Resource Conservation and Recovery Act
    - RCRA Regulations 40 CFR Parts 260-268
    - Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
    - Connecticut Hazardous Waste Management Regulations, Title 22a, Chapter 449

    ii. Barceloneta facility:
    - Federal Clean Air Act and Regulations
    - Puerto Rico State Implementation Plan
    - Resource Conservation and Recovery Act
    - RCRA Regulations 40 CFR Parts 260-268
    - Puerto Rico Public Law No. 9, Regulation for the Control of Hazardous and Non-Hazardous Waste, Part III, Section 302, and Part IV, Sections 402, 404 and 405

    iii. Brooklyn facility:
    - Federal Clean Air Act and Regulations
    - New York State Air Pollution Regulations, Title 6, Chapter III, Subchapter A, Parts 201 through 212 and Part 233

    iv. Ringaskiddy facility:
    - Requirements for Integrated Pollution Control License, EPA

3. Aqueous.- Emissions will be in compliance with the following requirements:

   i. Groton facility:
   - Federal Clean Water Act
   - 40 CFR Parts 124 and 125 (Federal Clean Water Regulations)
   - Connecticut General Statutes Title 22a, Chapter 446k, Water Pollution Control
   - Connecticut DEP Discharge Permit Regulations, Title 22a, Chapter 430
   - Connecticut General Permit for Stormwater Discharge, Title 22a, Chapter 430B

   ii. Barceloneta facility:
   - Federal Clean Water Act
   - Federal Clean Water Regulations, 40 CFR Parts 124 and 125
   - Puerto Rico Water Pollution Control Law, Laws of Puerto Rico Annot., Title 24, Chapter 35
   - Puerto Rico Water Quality Standards, Environmental Quality Board, Article 1-10

   iii. Brooklyn facility:
   - Federal Clean Water Act
   - Federal Clean Water Regulations, 40 CFR Parts 124 and 125
   - New York City Charter, Section 1105, Administrative Code of New York City, Section 1403, Section 683e, Sections 687 and 689, New York City Bureau of Water Pollution Control
   - New York City DEP Commissioner's Order and Directive for Effluent Pre-treatment, dated September 12, 1990

   iv. Ringaskiddy facility:
   - Requirements for Integrated Pollution Control License, EPA

4. Terrestrial.- Non-hazardous and hazardous waste emissions will be in compliance with the following requirements:

   i. Groton facility:
   - Resource Conservation and Recovery Act
   - RCRA Regulations 40 CFR Parts 260-268
   - Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
   - Connecticut Solid Waste Management Regulations, Title 22a, Chapter 209
   - Connecticut Hazardous Waste Management Regulations, Title 22a, Chapter 449

ii. Barceloneta facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- Puerto Rico Public Law No. 9, Regulation for the Control of Hazardous and Non-Hazardous Waste, Part III, Section 302, and Part IV, Sections 402, 404 and 405

iii. Brooklyn facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- New York Solid and Hazardous Waste Management Laws, New York Consolidated Laws Service, Environmental Conservation Law, Article 27
- New York Hazardous Waste Regulations, New York Compilation of Rules and Regulations, Title 6, Chapter 370, 371 and 372

iv. Ringaskiddy facility:
- Requirements for Integrated Pollution Control License, EPA

Appendix 1 cont'd

Applicable Permit/License Numbers, Issuing Authorities and Expiration Dates

Permits for Brooklyn Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Water	NYC DEP	Commissioner's Order/ Directive	May 4, 2000
Air	NYC DEP	PA530-93J	Approval pending
	NYC DEP	PA533-73Y	May 11, 1997
	NYC DEP	PA537-73N	May 19, 1997
	NYC DEP	PA237-92L	May 12, 1996. Continues in effect until new permit issues.
	NYC DEP	PA233-95H	March 21, 1996 Continues in effect until new permit issues.

Permits for Groton Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Water	CT DEP	NPDES Permit # CT0000957	July 30, 1996 Continues in effect until new permit issues.
Air	CT DEP	Permit to Operate #0081	Issued December 14, 1995. No Designated Expiration Date
Air	CT DEP	RACT Order 8021	Issued August 15, 1995. No Designated Expiration Date

Permits for Ringaskiddy Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Air, Water	EPA	Integrated Pollution Control	Issued May 18, 1995
Waste	EPA	License #13	No designated expiration date

Permits for Barceloneta Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Water	(1) PRASA (Puerto Rico Aqueduct Authority) (2) AFICA (Puerto Rico Industrial, Medical, and Environmental Pollution Control Facilities and Financing Authority)	Facility Agreement	Bonds mature August 1, 1998, but Entitlements do not expire.
Water	PRASA	Pretreatment Permit	May 23, 1998
Air	EQB	Air Permit PFE 09-1393-0282-I-II-III-0	Effective July 7, 1993. (Continues in effect until issuance of Title V permit.)

Appendix 2

Abbreviated Environmental Assessment.

Ben Venue Laboratories, Inc.

ABBREVIATED ENVIRONMENTAL ASSESSMENT

1.0 DATE

January 31, 1995

2.0 NAME OF APPLICANT

Ben Venue Laboratories, Inc.

3.0 ADDRESS

270 Northfield Road
Bedford, OH 44146

4.0 DESCRIPTION OF THE PROPOSED ACTION

Ben Venue Laboratories, Inc. proposes to formulate, aseptically fill and seal , at its facility in Bedford, Ohio, the drug product Zanthromax (Azithromycin for Injection, Intravenous) for Pfizer, Inc. This manufacturing site's environmental assessment information is being supplied as part of the abbreviated environmental assessment for NDA 50-733, as required by 21 CFR 25.31.

A. Description of the General Environment

Ben Venue Laboratories, Inc., is located in Bedford, Ohio, a city of approximately 15,000. The city is located in Cuyahoga County and is approximately 17 miles south of Cleveland, Ohio. Approximately 400 people are employed at the site. The surrounding land use consists of light industrial and chemical manufacturing and single family residential. The site is served by municipal water and sewer services. No additional construction or employment will result from the proposed action.

The climate is typical of a northern temperate zone with an average summer time temperature of 79° F in June and 15° F in January. Precipitation in the form of rain and snow averages 35 inches and 56 inches, respectively.

B. Air Resources

Air Quality in this area is in compliance with the National Air Quality Standards (NAQS) of the Clean Air Act for all air toxics except ozone. Cuyahoga County is in non-attainment with the NAQS for ozone. The State of Ohio Environmental

Protection Agency (Ohio EPA) is responsible for implementing the state air quality implementation plan.

C. Water Resources

All process waters used at the site are supplied by the Bedford Municipal Water Authority. The facility uses approximately 150,000 gallons per day on average throughout the year. Daily water use varies depending upon production needs. Approximately 15 percent, or 22,500 gallons per day are lost through evaporation and the remaining 122,500 gallons discharged to the sanitary sewer. Wastewater discharged from the site is received by the City of Bedford's Publicly Owned Treatment Works (POTW). Ben Venue Laboratories, Inc. holds a permit for indirect discharge to the POTW under the National Pollutant Discharge Elimination System. Storm water drainage from the site enters Tinkers Creek, a minor tributary of the Cuyahoga River. Ben Venue holds a Storm Water General Permit, number 3GR002998, administered by the Ohio EPA.

D. Land Resources

The manufacturing facility is located on approximately 8.4 acres of land and comprises two major buildings with about 225,000 square feet of floor space. The topography of the site is generally flat to slightly sloping. Soil is silt-clay typical of the northern Ohio region.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The preparation of this drug product involves the formulation of the liquid materials, sterile filling, and sealing the vials. The chemicals used in the filling operation are listed below:

Chemicals:

Ingredient	Grade	mg/mL	Use
Azithromycin Dihydrate for Parenteral Use	Pharm	524.1	active ingredient
Citric Acid, Anhydrous	USP	384.6	buffer
Sodium Hydroxide	NF	198.3	adjust pH
Water for Injection	USP	5548	processing aid, evoparated during processing
Nitrogen	NF	------	inert atmosphere

For Cleaning:	Water, Tap Water, Purified USP Water for Injection, USP Cleaner
Product Name:	Zithromax (Azithromycin for Injection Intravenous)
Chemical Name:	13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,7,10,12,14-heptamethyl-11-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one
Molecular Weight:	750.00

Cleaning agents used in the production process are water and industrial cleaners typical of a pharmaceutical manufacturing facility.

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Expected emissions, emission controls, occupational safety standards and compliance with environmental laws and regulations are discussed below.

A. Air Emission Controls

Air emissions from the manufacture of the drug product may include trace particulates. All work areas used in the manufacture of the drug product are vented to High Efficiency Particulate Filters (HEPA). These filters are expected to capture at least 97 percent of any particulates entering the air in the work space. Filtered air is vented to the outside. The filters are monitored on a schedule that varies with production activity because of the multiproduct nature of the manufacturing site. Filters no longer meeting control specifications enter the solid waste stream from the facility.

No air emission permits are required for the facility by either state or federal authorities due to the nature and low volume of emissions. No volatile organic solvents are used in this production process, all solvents are water based. A small amount of alcohol and bleach is used for sanitization. The emission from this use are expected to be negligible. Three boilers are registered by the Ohio EPA: 1318030726B001, 1318030726B002, and 131080307296B003. There is no date of expiration for the boilers' registration.

B. Liquid Wastes and Emission Controls

Liquid waste from the production process are expected to consist of production equipment rinses and tailings left over from the filling operation. Prior to rinsing, all equipment is vacuumed to remove any solid material left. The vacuumed material is considered toxic and is handled as toxic waste. Both the vacuumed material and the rinse material from the production of the drug product are collected by Ben Venue Laboratories and disposed of by an EPA licensed contractor, Chemical Analytics, Inc.

As noted above, Ben Venue holds a permit for indirect discharge to the Bedford POTW. The permit (3PD00005101*BP) is administered by the Ohio EPA in accordance with the Clean Water Act and Rule 3745-33-06 of the Ohio Administrative Code. It requires the monitoring of discharge flow rate, pH, and cyanide concentrations at 3 to 6 month intervals. The discharge pH is limited to a pH of not less then 5.0 at any given time. Cyanide discharge concentrations are limited to not more then 1.63 mg/liter CN on a daily basis. Flow rate is not limited. The permit was updated on September 13, 1994 and expires on December 31, 1999. The proposed action is expected to have no effect on this permit because of the limited volume of waste entering the sanitary sewer and the fact that no cyanide is used in this production process.

Liquid wastes, including some liquid tailing wastes from the filling operation as well as liquid wastes from the quality control laboratory will be collected in 55 gallon drums and disposed of by a licensed contract waste disposal firm. Ben Venue Laboratories, Inc. holds identification number OHD091625749 under the Resource Conservation and Recovery Act. The contract waste disposal firms address and EPA identification numbers are given below:

Chemical Analytic, Inc.
27982 Beverly
Romulus, MI 48174

US EPA I.D.: MID985568021
MIP000000357

The operations of Chemical Analytics, Inc. And the disposal firms that they use, are audited by Ben Venue Laboratories, Inc. personnel on an annual basis. Chemical Analytics will use on of the two disposal facilities to process waste waters for ultimate disposal. These include:

1. Chem-Tron
35850 Schneider Ct.
Avon, OH 44146
US EPA I.D.: OHD066060609

Chem-Tron collects aqueous waste streams, cracks of any residual organic solvents that may be present and then ships the waste waters to Research Environmental Industries (US EPA ID#: OHD004178612) which is located at 2777 Broadway Avenue, Cleveland, OH 44115. Research Industries then treats waste waters to remove solids and then disposes solids via appropriate means (landfill or hazardous waste incinerator) and water is discharged to the sanitary sewer for the City of Cleveland POTW.

2. CHEM-MET Services, Inc.
18550 Allen Road
Wyandotte, MI 48192
US EPA I.D.: MID096963194

Waste water is treated via neutralization, stabilization and solidification and is then sent to sanitary landfills managed by Chemical Waste Management.

Rinse waters from the first rinse of production equipment are collected and treated by evaporative de-watering on site before being disposed by Chemical Analytics.

C. Solid Waste Controls

Non-Hazardous solid wastes such as paper, aluminum, plastic, filters and disposable suits and lab ware that cannot be recycled are disposed of in a state licensed land fill.

Toxic solid wastes, including rejected raw materials and finished product, severely contaminated HEPA filters and quality control laboratory wastes are disposed via incineration by a facility permitted to handle such waste streams. The disposal is managed under contact by:

Medical Tracking Systems
607 Freedlander Road
Wooster, OH 44691

Transporter Registration Number: 85-T-00013.

In order to minimize the amount of material for disposal, excess drug product may be returned to the customer for further use.

D. Employee Protection

All necessary steps are taken to comply with the Occupational Safety Act of 1971, the Hazards Communication Standard of 1985 and Title 29 of the Code of Federal Regulations Part 1910. Material Safety data Sheets (MSDS) are available on-site for all chemicals used in the production process. Employees associated with production have the appropriate MSDS's available for their review. Appropriate protective clothing including uniforms, gloves, safety glasses, hard hats and individual respirators are available. Employees receive on-going training on safe work habits and adherence to safety protocols are strictly enforced. In the event of an emergency, the site specific emergency response plan would be implemented to protect workers and the environment.

E.. Compliance Statement

By signing this environmental assessment, Ben Venue Laboratories, Inc. confirms that it is in compliance with all applicable emission requirements set forth in permits, consent decrees and administrative orders, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations at its facility discussed above.

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

This item is intentionally omitted as permitted by 21 CFR 25.31 a(b)3(ii)

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

This item is intentionally omitted as permitted by 21 CFR 31 a(b)3(ii)

9.0 USE OF ENERGY AND RESOURCES

This item is intentionally omitted as permitted by 21 CFR 31 a(b)3(ii)

10.0 MITIGATION MEASURES

This item is intentionally omitted as permitted by 21 CFR 31 a(b)3(ii)

11.0 ALTERNATIVES TO THE PROPOSED ACTION

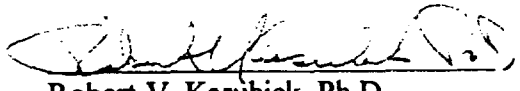
This item is intentionally omitted as permitted by 21 CFR 31 a(b)3(ii)

12.0 List of Preparers:

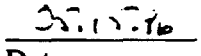
Valerie Baker, C.S.P. Ben Venue Laboratories, Inc., Safety, Health and Environmental Engineer. Six years of experience in the development and administration of occupational safety, health and environmental programs. She holds a Bachelor of Science degree from Indiana University of Pennsylvania in Safety Sciences.

13.0 CERTIFICATION

The undersigned responsible officials certify that the information presented in this document is true, accurate, and complete, to the best of the knowledge of Ben Venue Laboratories, Inc.



Robert V. Kasubick, Ph.D.
Vice President of Regulatory Affairs
Ben Venue Laboratories, Inc.



Date

EA located in Docket 93N-0185

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-670

ZITHROMAX (azithromycin)

Pfizer Central Research has made a New Drug Application for Zithromax (azithromycin) a macrolide systemic antibiotic. Chemically, azithromycin is 9-deoxo-9a-aza-9a-methyl-9a-homo-erythromycin A. Zithromax capsules are formulated to contain 250 mg azithromycin.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Azithromycin, Pfizer has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of Azithromycin or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

DEC 17 1991

DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/12/91

DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental assessment for Zithromax.
Package Insert

CC: Original NDA 50-670
Philip Chao HFD-382
Fonsi File 50670

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 1, 1996

FROM: Nancy Sager

SUBJECT: EA for NDA 50-733 and 50-719

TO: Jim Timper

I am returning the environmental assessment reviews for NDA 50-733 and 50-719 for the following reasons:

General:

1. The reviews should have the concurrence of your supervisor. Although I look at reviews, I do not sign-off on them.

2. However, I do sign-off on the FONSI and each consult should have one. Instructions and examples are on the common drive (x:\cmccc\nepacom\fonsi.gui)

3. One of the items that should be addressed in the review is relating the toxicity data to the expected environmental concentration and concluding whether significant environmental impacts are expected.

Specific comments:

NDA 50-719:
I read the EA and do not have any problems with the EA submitted. I noticed in your review that you call it an abbreviated EA but it really is an EA under 25.31.a(a). I would suggest that in the FONSI you mention that the products in the kit are all currently being manufactured for commercial distribution as individual products.

NDA 50-733:
I noticed in your review that you call it an abbreviated EA but it really is an EA under 25.31.a(a). I read the EA and have the following comments:

1. The EA does not appear to be an FOI version (production volumes included).

2. This product will be manufactured by a company not included in the referenced original Azithromycin EA for NDA 50-670. The applicant only provides the address and a statement that the firm is in compliance. Since this manufacturing site wasn't in the original EA for NDA 50-670 the information to fulfill format items 6a, 6b and 6d also have to be included (see industry guidance). The company should authorize the rerelease of the FOI EA of NDA 50-670.

Give me a call if you have any questions.

c.c.
EA file NDA 50-719
EA file NDA 50-733

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Robert B. Clark
Senior Associate Director

February 5, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective
Drug Products (HFD-520)
Attention: Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Zithromax (azithromycin for intravenous injection)
New Drug Application - NDA 50-733

Dear Dr. Fanning:

Pursuant to 21 CFR 314, we are submitting a New Drug Application for Zithromax (azithromycin for intravenous injection) for the treatment of patients with community-acquired pneumonia (CAP) or pelvic inflammatory disease (PID) who require initial intravenous antibiotic therapy. This NDA has been assigned number NDA 50-733 by the Central Document Control Room.

Zithromax (azithromycin) Capsules have been approved previously for use in the treatment of respiratory tract infections, skin and skin structure infections and *Chlamydia trachomatis* genitourinary infections in patients 16 years of age and older (NDA 50-670, approved on November 1, 1991). NDA 50-693 (approved September 28, 1994) provided for a single 1 gram dose packet. On October 19, 1995 Zithromax (azithromycin for oral suspension) was approved for the treatment of acute otitis media and streptococcal pharyngitis/tonsillitis in pediatric patients (NDA 50-710). The chemistry, manufacturing, and controls data and methods validation package contained in the original Zithromax capsules NDA 50-670 are directly applicable to this NDA and are incorporated by cross-reference. Nonclinical pharmacology and toxicology data, as well as microbiological data contained in NDA 50-670 are also incorporated into this application by cross-reference.

In the original NDA submission for Zithromax capsules (NDA 50-670), data were included to support a claim of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient therapy. Although these two microorganisms are the most commonly encountered pathogens in patients with community-acquired pneumonia, a large percentage of patients exhibit CAP due to *Mycoplasma*

pneumoniae, Chlamydia pneumoniae or *Legionella pneumophila.* A supplemental application (filed on December 28, 1995) to NDA 50-670 provided data supporting the use of orally administered Zithromax capsules in the treatment of outpatients with CAP due to *M. pneumoniae* or *C. pneumoniae.*

A sub-population of patients with CAP or PID require hospitalization and intravenous antibiotic therapy. These patients are more severely ill or cannot tolerate oral therapy. It is common medical practice to initiate intravenous antibiotic therapy for these patients and when their condition warrants, replace IV medication with an oral agent.

Support for the use of Zithromax for Intravenous Injection in the treatment of hospitalized patients with community-acquired pneumonia is derived from five clinical trials. Two of these trials were performed in the U.S. In the first study (Protocol 93CE33-0618), hospitalized patients with CAP received single daily doses of azithromycin (IV followed by oral therapy) or cefuroxime (IV followed by oral therapy) to complete 7-10 days of treatment. Erythromycin was added to the comparative regimen at the discretion of the investigators to provide coverage of atypical pathogens. For the 268 patients seen at 10-14 days post-therapy, the clinical success rate (i.e., cure plus improvement) was 77% for azithromycin and 74% for the comparative regimen. For the 252 patients who were evaluated at 4-6 weeks post-therapy, the cure rate was 75% for the azithromycin group and 71% for the comparative group.

A second noncomparative clinical and microbiologic trial in 94 hospitalized patients with CAP (Protocol 93CE33-0625) confirmed these results. The combined clinical success rate for the 84 patients seen at the 10-14 day post-therapy visit was 88% for azithromycin (regimen as described above). For the 85 patients who were evaluated at 4-6 weeks post-therapy, the cure rate was 86% (73/85) for azithromycin.

In addition to the data from the U.S. trials discussed above, data from three non-U.S. studies in CAP sponsored by Pfizer (Protocols 066-349, 066-350 and 066-359) support the safety and efficacy profile of intravenously administered azithromycin observed in the U.S. studies.

Zithromax for Intravenous Injection was also demonstrated to be effective in the treatment of women with PID. In a controlled comparative clinical and microbiological study in PID (Protocol 066-341), azithromycin monotherapy (single IV dose followed by oral therapy for 6 days) was compared to combination azithromycin (dosage regimen as described) with metronidazole (single IV dose followed by oral therapy for 11-12 days), and to metronidazole (dosage regimen as described) with oral doxycycline (14 days) and cefoxitin (single IV/IM dose with probenecid). The combined clinical success rate (cure plus improved) at the last observation was 93% (69/74) for azithromycin monotherapy versus 97% (77/79) for azithromycin/metronidazole versus 90% (69/74) for the metronidazole/ doxycycline/cefoxitin standard regimen.

Mary Fanning, M.D., Ph.D., Director
NDA 50-733/Zithromax for Intravenous Injection
February 5, 1996

PID

(2)

A second controlled comparative trial confirmed the efficacy and safety of azithromycin in the treatment of PID. In this study (Protocol 066-342), azithromycin monotherapy (single IV dose for 2 days followed by oral therapy for 5 days) was compared to combination azithromycin (dosage regimen as described) with metronidazole (single IV dose for 2 days followed by oral therapy for 10-12 days), and to oral doxycycline (21 days) with amoxicillin-clavulanic acid (IV for 16 days). The combined clinical success rate at the last observation was 93% (27/29) for azithromycin monotherapy versus 81% (21/26) for azithromycin/metronidazole versus 83% (20/24) for the comparative regimen.

Based on the information presented in this submission, intravenous azithromycin (followed by oral therapy) has been demonstrated to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus* or *Streptococcus pneumoniae,* or pelvic inflammatory disease due to *Bacteroides bivius, Chlamydia trachomatis, Mycoplasma hominis, Neisseria gonorrheaea, Peptostreptococcus spp., Streptococcus agalactiae or Ureaplasma urealyticum* in patients who require initial intravenous therapy. Microbiological data from the clinical studies presented herein establish the fact that azithromycin provides coverage for each of the causative pathogens in these two infections.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this application, to the best of its knowledge, Pfizer Inc did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

In addition, the sponsor hereby certifies that an exact copy of the Chemistry, Manufacturing, and Controls section (field copy) of this submission has been provided to our FDA District Office (Brooklyn, New York).

Please be advised that the applicable user fee for this submission has been remitted in accordance with the Prescription Drug User Fee Act of 1992 and that Form 3397 is enclosed as required. The User Fee I.D. Number for this NDA is 2926.

We look forward to a timely review of this application. If there are any questions or comments regarding the organization or content of this supplemental application, please contact the undersigned at (212) 573-3412.

Sincerely,

Robert B. Clark

Robert B. Clark
Enclosures

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314)

Form approved : OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT	DATE OF SUBMISSION
Pfizer Inc	2/5/96
ADDRESS *(Number, Street, City, State, and Zip Code)*	TELEPHONE NO. (Include Area Code)
235 East 42nd Street New York, New York 10017	(212) 573-2323
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 50-733

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
azithromycin	Zithromax

CODE NAME (If any)	CHEMICAL NAME
	9-deoxo-9a-homoerythromycin A-(USAN)

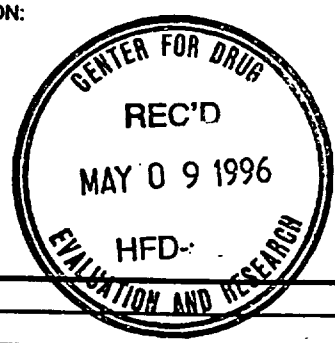
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Lyophilized Powder	For Intravenous Injection	100 mg/ml

PROPOSED INDICATIONS FOR USE

Community-Acquired Pneumonia
Pelvic Inflammatory Disease

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND	DMF
IND	DMF
IND	DMF
NDA 50-670	
NDA 50-693	
NDA 50-710	



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ RESUBMISSION APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL

☒ ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
X	2. Summary (21 CFR 314.50(c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Margaret A. Longshore, Ph.D., Director	M. A. Longshore	2/5/96
ADDRESS *(Street, City, State, Zip Code)* 235 East 42nd Street, New York, NY 10017		TELEPHONE NO. *(Include Area Code)* (212) 573-2556

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Pfizer Pharmaceuticals, Inc.
Rd. 2, Km. 58.2, P.O. Box 628
Barceloneta, P.R. 00617

Pfizer

Pharmaceuticals

Lou DeBergalis
Quality Control Operations Manager

May 15, 1996

Ms. Myriam M. Sosa
Food and Drug Administration
P. O. Box 5719
San Juan, PR 00906-5719

Dear Ms. Sosa:

The purpose of this letter is to clarify the Pfizer production sites manufacturing azithromycin dihydrate drug substance that is to be utilized in azithromycin for intravenous injection drug product. The information below summarizes both our discussions of May 14, 1996 while you were at our Barceloneta site, and the telephone conversation between you and Carmen Recondo later that same day.

The New Drug Application for this injectable dosage form of azithromycin (NDA 50-733, filed on February 5, 1996) referred to the original NDA for azithromycin capsules (NDA 50-670, approved November 1, 1991) for information regarding the drug substance process and sites. In addition to this cross-reference, the final recrystallization step using purified process water (low endotoxin) was described in NDA 50-733.

The original azithromycin capsule NDA (NDA 50-670) described the sites of manufacture of azithromycin dihydrate drug substance, including Barceloneta. However, as discussed with you, Pfizer will not perform the final recrystallization step utilizing purified process water (low endotoxin) for the drug substance to be used in azithromycin for intravenous injection (NDA 50-733) at our Barceloneta site, and this site will be withdrawn as a manufacturing site of azithromycin dihydrate drug substance from NDA 50-733. An amendment to NDA 50-733 for azithromycin for intravenous injection will be submitted to clarify the site that will perform the drug substance processing required for the azithromycin intravenous drug product.

The Barceloneta site will continue to manufacture all other steps of azithromycin dihydrate drug substance for use in non-parenteral (i.e. oral) azithromycin dosage forms.

Please contact me at 846-4300, ext. 2700 if you have additional questions on this matter.

Sincerely,

Lou DeBergalis

4. Manufacturing Processes

4.1 Manufacturing/Packaging Sites

Azithromycin for Injection 500 mg/vial (100 mg/mL) will be manufactured, packaged and labeled at the following site:

Azithromycin for Injection 500 mg/vial (100 mg/mL) will be tested (approval and stability testing) at either of the following sites:

Pfizer Inc
Quality Control Division
630 Flushing Avenue
Brooklyn, NY 11206

Pfizer Inc
Quality Control Division
Eastern Point Road
Groton, CT 06340

DUPLICATE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3112 Fax 212 573 1563

Robert B. Clark
Senior Associate Director

January 13, 1997

NEW CORRESPONDENCE

David Feigal, Jr., M.D., M.P.H., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-733 ZITHROMAX® (azithromycin for intravenous injection)
Submission of Revised Draft Labeling for Comment

Dear Dr. Feigal:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin for intravenous infusion) NDA 50-733. Further reference is made to a January 13, 1997 facsimile of draft labeling for the above application. Attached please find hard copy of this draft labeling.

Pfizer looks forward to discussing this labeling with the division at the meeting scheduled for January 30, 1997 at 8:15 am at 9201 Corporate Blvd, Rockville, Maryland.

It should be noted that this labeling incorporates all pertinent revisions agreed upon with the division and contained in the final printed labeling (FPL) submitted on January 13, 1997 to NDA 50-670, NDA 50-710 and NDA 50-711. Questions on the attached should be directed to the undersigned.

Please include this information in the subject file.

Sincerely,

Robert B. Clark

REVIEWS COMPLETED
ACTION
LETTER E-MAIL FAX
MINUTES DATE

cc: Hard Copy plus disk -Jose Cintron, Senior Regulatory Project Manager (HFD-520)

DUPLICATE

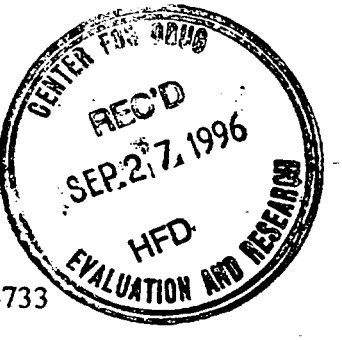
Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

September 26, 1996 NEW CORRESPONDENCE

Robert B. Clark
Senior Associate Director

David W. Feigal, Jr., M.D., MPH, Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE



RE: ZITHROMAX® IV (azithromycin for intravenous injection) NDA 50-733
Response to Division Request for Information

Dear Dr. Feigal:

Reference is made to our pending New Drug Application for ZITHROMAX® IV (azithromycin for intravenous injection), NDA 50-733, submitted on February 5, 1996.

During a September 9, 1996 teleconference between representatives from the Division of Anti-Infective Drug Products (Dr. G. Girardi, Dr. S. Bell and Mr. J. Cintron) and Pfizer, Pfizer was requested to provide FDA with additional information concerning the previously submitted (May 31, 1996 submission) electronic version of certain sections of the application.

Enclosed are five (5) computer disks (scanned for viruses) containing the SAS data sets for the clinical studies identified as pivotal (for efficacy) in the submission. These include the U.S. community acquired pneumonia studies -0618 and -0625 as well as the non-U.S. pelvic inflammatory disease studies 341 and 342. An explanatory document is also appended to this letter as well as the output (SAS PROC CONTENTS) which describes the SAS data sets listing the variables, variable types, and variable labels. For each data set, the first 25 observations have been printed. In addition, the attached hard copy containing the first 25 data sets for non-U.S. PID studies 341 and 342 only lists data for study 341; data for 342 are of course included on the relevant disk. Please note, all variables which reference a Pfizer FORMAT or DICTIONARY Library have been decoded. Even though references to Pfizer Dictionaries and Format Libraries have been removed from the data sets, it is recommended that when the files are read into SAS that the NOFMTERR (no format error) option is invoked.

Please note that the enclosed will be discussed during a meeting planned for Thursday September 26, 1996 with Drs. Girardi, Bell and Mr. Cintron at 3 pm at your offices. Also to be discussed at the time are the overall format and content of this application so that the Reviewers may seek additional clarification regarding the location in the application of data they deem critical.

Questions on the attached should be directed to the undersigned.

Please include this information in the subject file.

Sincerely,

Robert B. Clark

cc: Mr. Jose Cintron, Project Manager (HFD-520) - Disks Included
Mr. Kenneth Edmunds, Jr. (HFD-76)

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

DUPLICATE

DRUG AMENDMENT

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Robert B. Clark
Senior Associate Director

August 20, 1996

David Feigal, Jr., M.D., M.P.H., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-733
ZITHROMAX® (azithromycin for intravenous injection)

Dear Dr. Feigal:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin for intravenous injection) NDA 50-733, filed on February 5, 1996.

Enclosed please find the four-month safety update for this pending application. The information contained in the attached is consistent with the safety data as submitted in the original application.

Questions on the attached should be directed to the undersigned. Please include this information in the subject file.

Sincerely,

Robert B Clark

Robert B. Clark

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

ORIGINAL

NEW CORRESP

NC

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Pfizer

May 30, 1996

Robert B. Clark
Senior Associate Director

N AI
6-3-96
JHE

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ [illegible] ☐ [illegible]
CSO INITIALS DATE

RE: NDA 50-733
ZITHROMAX® (azithromycin for intravenous injection)

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin for intravenous injection), NDA 50-733, submitted on February 5, 1996.

During a March 27, 1996 teleconference between representatives from the Division of Anti-Infective Drug Products and Pfizer, Pfizer was requested to provide FDA with an electronic version of certain sections of the supplement to facilitate the review. The requested information is enclosed in five (5) computer disks (scanned for viruses). An explanatory document is also appended to this letter. Questions on the attached should be directed to the undersigned. SAS data sets requested by FDA are being provided under separate cover.

CENTER FOR DRUG REC'D MAY 30 1996 HFD- EVALUATION AND RESEARCH

Please include this information in the subject file.

Sincerely,

Robert B. Clark

Robert B. Clark

cc: Mr. Jose Cintron, Project Manager (HFD-520) - Disks Included
Mr. Kenneth Edmunds, Jr. (HFD-76)

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

Trip

NEW CORRESP

NC

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Pfizer

Just
6/17/96

May 22, 1996

Robert B. Clark
Senior Associate Director

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective
Drug Products (HFD-520)
Attention: Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Zithromax (azithromycin for intravenous injection) NDA 50-733
CMC Section Clarification

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for Zithromax (azithromycin for intravenous injection), NDA 50-733, submitted on February 5, 1996.

The purpose of this letter is to clarify the intended commercial source of "Azithromycin Dihydrate for Parenteral Use" drug substance for use in our recently submitted NDA (NDA 50-733), Zithromax for Injection (azithromycin for intravenous injection) drug product, filed on February 5, 1996.

At this time, the sole source of "Azithromycin Dihydrate for Parenteral Use" grade drug substance will be our Groton, Connecticut facility located at Eastern Point Road. In addition, the azithromycin dihydrate utilized in the preparation of the parenteral grade drug substance will continue to be sourced from those sites approved in our original NDA for Zithromax Capsules (NDA 50-670).

If there are questions on this information, please contact the undersigned at (212) 573-3412. Please include this information in the subject file.

Sincerely,

Robert B. Clark

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

cc: J. Timper, Reviewing Chemist (HFD-520)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

DUPLICATE

July 17, 1996

Robert B. Clark
Senior Associate Director

David Feigal, M.D., Acting Director
Division of Anti-Infective
Drug Products (HFD-520)
Attention: Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Zithromax (azithromycin for intravenous injection) NDA 50-733

Dear Dr. Feigal:

Reference is made to our pending New Drug Application for Zithromax (azithromycin for intravenous injection), NDA 50-733, submitted on February 5, 1996.

During preparation of the four month safety update for this application, it has come to our attention that a single page was inadvertently omitted from Volume 51. Attached is a copy of Table 6.6 entitled: "Listing of Patients Discontinued Due to Adverse Events of Laboratory Abnormalities - All Treated Patients – Study Drug = Azithromycin" for protocol #93-CE33-0625. This page (numbered as "8 4622A") should be inserted in Volume 51 between pages 8 4622 and 8 4623. We apologize for this oversight.

If there are any questions on this issue, please contact the undersigned at 212 573-3412.

Sincerely,

Robert B. Clark
Enclosure

cc: Mr. Jose Cintron, Project Manager (HFD-520)

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

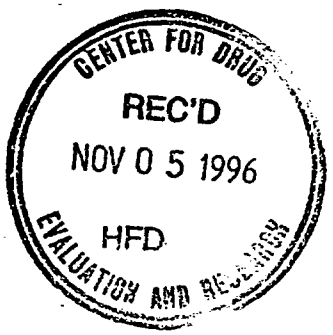
DUPLICATE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

BC
NDA ORIG AMENDMENT

October 30, 1996

Robert B. Clark
Senior Associate Director



David W. Feigal, Jr., M.D., MPH, Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: ZITHROMAX® IV (azithromycin for intravenous injection) NDA 50-733
Response to Division Request for Information - Environmental Assessment

Dear Dr. Feigal:

Reference is made to our pending New Drug Application for ZITHROMAX® IV (azithromycin for intravenous injection), NDA 50-733, submitted on February 5, 1996.

Further reference is made to a August 16, 1996 request from Ms. Nancy Sager (HFD-357) for a revised Environmental Assessment for the above pending application. The requested information is enclosed.

Questions on the attached should be directed to the undersigned. Please include this information in the subject file.

Sincerely,

Robert B Clark

Robert B. Clark

cc: Mr. Jose Cintron, Project Manager (HFD-520) - cover letter only
Ms. Nancy Sager (HFD-357) - full set

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE