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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-784

Medical Review(s)

CLINICAL REVIEW

Medical Officer's Review of NDA 50784

Azithromycin (ZITHROMAX®) 500 mg for 3 days

Indication: Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis

Applicant: Pfizer Incorporated

Medical Reviewer: Alma C. Davidson, M.D.
Medical Officer
DAIDP, HFD-520

CLINICAL REVIEW

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CLINICAL REVIEW

A. Executive Summary

I. Recommendations

Based on the review of efficacy and safety data submitted by the applicant, it is the recommendation of the medical reviewer that azithromycin (ZITHROMAX®) 500 mg administered orally for 3 days in the treatment of acute bacterial exacerbation of chronic bronchitis be approved.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

There is a 250-mg tablet formulation approved for treatment of a variety of infections of infections using a 5-day regimen. In this New Drug Application (NDA), the applicant (Pfizer, Inc.) is seeking approval for a new formulation of azithromycin (500 mg tablets) for use in a new 3-day regimen.

The original adult clinical program for the 3-day regimen of azithromycin included [redacted] acute bacterial exacerbation of chronic bronchitis (ABECB), [redacted] The applicant submitted study A0661013 on July 27, 2001 as part of the adult accelerated (3-day regimen of azithromycin) clinical program to support the claim in the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB).

[redacted]. Study A0661013 is a randomized, double-blind, comparative, and multicenter trial consisting of both male and female subjects between the ages of 35 and 75 years with ABECB. The subjects received either oral azithromycin 500 mg/day as a single daily dose for 3 days or oral clarithromycin 1000 mg/day divided as 500 mg morning and evening doses for 10 days. Subjects were followed for 21-24 days. The data from three principal investigators including [redacted] were excluded from the efficacy analysis per Division of Scientific Investigations (DSI) recommendations due to concerns about data integrity.

B. Efficacy

There were two populations analyzed in the study including: (1) modified-intent-to treat (MITT), defined as subjects who had taken at least one dose of study medication, had a confirmed diagnosis of ABECB and had a purulent sputum, i.e., WBC>25 and <10 squamous cells/lpf, and (2) per protocol (PP) evaluable which included MITT subjects who had received 80-120% of protocol specified doses of active therapy and had visits in the appropriate time schedule. The objective of the study was to show equivalence between the success rates of the two treatments. The primary measure of efficacy was based on the investigator assessment of the clinical outcome at the *Test-of cure* (TOC) visit. The secondary efficacy response variable was bacteriological outcome. There were three scheduled study visits including Baseline (Visit 1; Day1), End of Therapy (Visit 2; Day 10-12) and Test of cure (Visit 3; Day 21-24). The follow-up visit (1-2 weeks after TOC) was required in the applicant's study protocol only if the investigator's clinical assessment was improved at TOC visit. At TOC, the applicant's clinical outcomes were cure and failure. If the investigator chose improvement at TOC, the subject was required to return for a follow-up visit within 1-2 weeks, and the investigator assigned cure or failure then. After exclusion of subjects from study sites of [redacted] the total randomized and treated population was 318 subjects. The total number of clinical MITT evaluable subjects was 306 (149 in the azithromycin treatment group and 157 in the clarithromycin treatment group) per applicant's analysis at TOC visit. There were 127/149 (85.2%) subjects who were cured at TOC in the azithromycin treatment arm and 129/157 (82.1%) subjects cured at TOC in the clarithromycin arm. The two-sided 95% confidence interval between the two treatment groups is [-6%, 12.0%]. In the PP population at TOC visit, the cure rates were as follows: 118/140 (84.2%) in the azithromycin treatment group and 121/145 (83.4%) in the clarithromycin treatment group with two-sided 95% CI of [- 7.7%, 9.4%].

The medical reviewer efficacy analysis included a total of 304 evaluable subjects in the clinical MITT population at TOC visit with 125/147 (85.0%) subjects cured in the azithromycin treatment arm and 129/157 (82.1%) subjects cured in the clarithromycin treatment arm, two-sided 95% confidence interval between the two treatment groups is [-6%, 12%]. Two subjects were deemed unevaluable per reviewer's random sample analysis. In the PP subset analysis at TOC, the cure rates were as follows: 115/138 (83.3%) in the azithromycin treatment group and 120/145 (82.7%) in the clarithromycin treatment group with two-sided 95% CI of [-8.9%, 10.0%].

The reviewer concurs with the applicant's MITT bacteriological efficacy analysis. The MITT bacteriological response by subject outcome at TOC is as follows:

eradication/presumed eradication in 48/56 (85.7%) subjects in the azithromycin treatment group and eradication/presumed eradication in 45/56 (80.3%) in the clarithromycin treatment group, with a 2-sided 95% CI of [-10.4%, 21.1%]. In the PP subset population, bacteriological response by subject at TOC is as follows: 45/53 (84.9%) subjects had a response of eradication/presumed eradication in the azithromycin treatment group while 43/53 (81.1%) subjects had a response of eradication/presumed eradication in the clarithromycin treatment group with a 2-sided 95% CI of [-12.5%, 20%].

The MITT clinical outcome by baseline pathogen at TOC is as follows: *S. pneumoniae*, 29/32 (90.6%) subjects with success in the azithromycin treatment group, and 21/27 (77.8%) subjects with success in the clarithromycin group; *H. influenzae*, 12/14 (85.7%) subjects with success outcome in the azithromycin treatment group and 14/16 (87.5%) subjects with success in the clarithromycin group; and *M. catarrhalis*, 11/12 (91.7%) subjects with success in the azithromycin group and 12/15 (80.0%) subjects with success in the clarithromycin group.

C. Safety:

The safety analysis included all subjects who received at least one dose of the study drug. The reviewer included all subjects who may have received at least one dose of the study medication from the original applicant's safety analysis (total of 404 subjects, 200 subjects in the azithromycin treatment group and 204 subjects in the clarithromycin treatment group). The incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 25% with azithromycin and 29% with clarithromycin. The most common side effects were diarrhea, nausea and abdominal pain with comparable incidence rates for each symptom of 5-9% between the two treatment arms. In the azithromycin treatment group, 73% of the treatment-related adverse events were classified as mild by the investigator and 1.3% were classified as severe. In comparison, 56% of the treatment-related adverse events attributed to clarithromycin were classified as mild and 9.6% were classified as severe by the investigator. There were no deaths reported in the azithromycin treatment group. One death occurred in the clarithromycin treatment group which was assessed by the investigator as not related to the study drug.

D. Dosing:

The approved dosage regimen for azithromycin includes a 500-mg loading dose (two 250-mg tablets) given in a single dose on day 1, followed by one 250-mg tablet daily on days 2-5. The new dosing regimen for azithromycin is 500 mg

given as a single tablet daily for 3 days in the treatment of acute bacterial exacerbation of chronic bronchitis.

B. Clinical Review

I. Introduction and Background

Azithromycin is the first antibiotic designated chemically as an azalide, a subclass of macrolide antibiotics. It differs in structure from the macrolide erythromycin by a methyl substituted nitrogen atom at position 9A of the lactone ring. As a result of the structural modification, azithromycin acquires properties that permit its rapid penetration into macrophages, fibroblasts, and polymorphonuclear cells. Azithromycin acts by binding to the 50s ribosomal subunit of susceptible microorganisms, interfering with microbial protein synthesis.

Azithromycin has been shown to be active *in vitro* against a broad spectrum of Gram-positive and Gram-negative bacteria, and atypical pathogens including those associated with infections of the lower respiratory tract. In vitro testing of azithromycin demonstrates antimicrobial activity against Gram-positive organisms such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*. In vitro activity is also observed against Gram-negative and intracellular bacteria including *Moraxella catarrhalis*, *Bordetella pertussis*, *Haemophilus influenzae*, *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila.*

Azithromycin is currently approved for the treatment of a variety of infections, including acute bacterial exacerbation of chronic obstructive pulmonary disease, community-acquired pneumonia, Group A streptococcal pharyngitis, otitis media, and uncomplicated skin and skin structure infections.

As part of the adult accelerated (3-day regimen) clinical program, the applicant submitted data to support acute exacerbation of chronic bronchitis (ABECB)

Primary efficacy for the claim of ABECB comes from a single pivotal study A0661013, which is the focus of this review.

CLINICAL REVIEW

A. Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

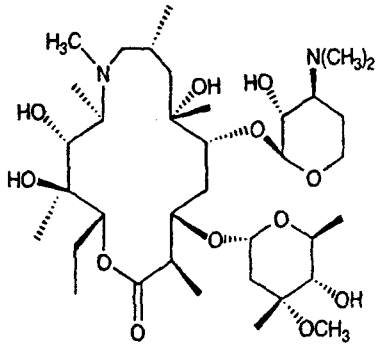
Azithromycin

Chemical Name: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*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)-β-*D-xylo* hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Azithromycin dihydrate:

Molecular formula: $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$ **Molecular weight**: 785.03

Structural formula (azithromycin base):



Proposed labeling submitted by applicant:

The following sections describe the changes which the applicant has requested be added to the label of Zithromax for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease.

- **The applicant proposes that the following labeling text (in bold characters) be added to the current "DOSAGE AND ADMINISTRATION" section :**

Adults:
The recommended dose of ZITHROMAX® for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease is: **either 500 mg per day for 3 days** or 500 mg as a single dose on the the first day followed by 250 mg once daily on Days 2 through 5.

- **The applicant proposes that under CLINICAL STUDIES section, the following text be added in the labeling as follows:**

Adult Patients

Acute Bacterial Exacerbations of Chronic Obstructive Pulmonary Disease

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Day 21- 24. For the [redacted] patients analyzed in the modified intent to treat analysis at the Day 21-24 visit, the clinical cure rate for 3 days of azithromycin was 85% [redacted] compared to 82% (129/157) for 10 days of clarithromycin [redacted]

The following outcomes were the clinical cure rates at the Day 21-24 visit for the bacteriologically evaluable patients by pathogen:

Pathogen	Azithromycin (3 Days)	Clarithromycin (10 Days)
S. pneumoniae	29/32 (91%)	21/27 (78%)
H. influenzae	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

Draft Labeling

B. State of Armamentarium for indication:

Many antibiotics, in several drug classes, are approved for the treatment of ABECB. Azithromycin itself is already approved for treatment of ABECB, but this application provides for the approval of a new 3-day dosage regimen.

C. Important Milestones in Product Development

- November 1991- Original NDA 50-670 (250 mg capsules) for azithromycin 500 mg on day 1 and 250 mg on days 2-4 gained approval for the adult indications currently listed in the package insert.
- July 10, 1998 - Pfizer submitted a proposal for submission of data to support an alternative dosing regimen for Zithromax in adults: 500 mg QD x 3 days. This regimen is approved in several foreign countries as an alternative to the 5 day regimen. For dosing in the pediatric population, a dosing regimen of 30 mg/kg or 60 mg/kg given over 3 days would be an alternative to the comparable 5 day dosing schedule.
- September 22, 1998 - Face-to-Face Meeting with Pfizer.The sponsor proposed the following claim structure: Adults: 500 mg/day x 3 days for acute exacerbation of chronic obstructive pulmonary disease, [redacted]
- May 13, 1999 - First Pre-NDA Meeting. Pfizer and the Division held a Pre-NDA meeting to discuss current plans for submission of the "3-Day" application.
- February 16, 2001 - Pfizer submitted pediatric efficacy supplements (NDA 50-710/S-008, S-009, S-010) for 3-day dosing for pharyngitis/tonsillitis and for 3-day dosing for acute otitis media.
- [redacted]
- July 27, 2001- Pfizer submitted NDA 50784 for Zithromax 500 mg tablets for 3 days in the treatment of adult [redacted] ABECB [redacted]

- [redacted]

- December 14, 2001 - Supplemental NDAs 50-710/S-008 and 50-710/S-009 for azithromycin oral suspension in the treatment of acute otitis media with a 1-day dosing and 3-day dosing regimens, respectively, were approved.

- [redacted]

- March 1, 2002 - Teleconference with Pfizer and DAIDP - in association with the Office of Drug Safety and DDMAC - raised several concerns with the proposed blister package of azithromycin 3-day dosing regimen. In appreciation of these concerns, Pfizer has revised the packaging for this accelerated dosing regimen giving it a new name of Zithromax TRI-PAK.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, other Consult reviews

- **Chemistry**

  There are no chemistry issues in this NDA submission. The chemistry, manufacturing and controls were acceptable. All the chemistry inspection sites findings were also acceptable. Please see the review of the chemistry reviewer, Dr. Andy Yu for details.

- **Animal Pharmacology and Toxicology**

  There were no new animal pharmacology/ toxicology data submitted in this application review according to the Pharmacology/toxicology reviewer, Kenneth Seethaler. However, the labeling of Zithromax in the Animal Toxicology section has been revised to reflect the addition of new text in the statement for "Phospholipidosis".

- **Microbiology**

  The bacteriological data for NDA 50-784 on *Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis* are "acceptable", according to the Clinical

Microbiology reviewer. Please see the Microbiology review by Harold Silver for details.

- **Biopharmaceutics**

The *in vitro* dissolution data revealed that Zithromax 500 mg tablet is bioequivalent to two 250-mg tablets. The applicant's dissolution data meets the requirements for a waiver of *in vivo* bioequivalence studies. Please see the review by Dr. Charles Bonapace, biopharmaceutics reviewer for details.

- **Statistics**

The statistical analysis concluded that azithromycin 500 mg per day for three days is equivalent in efficacy to treatment with clarithromycin 500 mg twice a day for ten days with respect to clinical outcome at TOC visit for acute exacerbation of chronic bronchitis. Please see the review by Dr. Mushfiqur Rashid for details.

- **Division of Scientific Investigations (DSI) Findings and Recommendations**

Due to concerns of data integrity from three study sites, including Drs.C. DeAbate, C. Mathew, S.Lerner and B. Schwart; DSI recommended that the data from these sites should be excluded from analysis in this study.

In addition, DSI assigned inspection of two domestic and two foreign sites in Study A0661013. The domestic sites inspection include sites for [redacted] DSI issued Form FDA 483 to [redacted] at the conclusion of the inspection. The items listed pertained to the need for strict adherence to reporting of adverse events. According to DSI, these items were not significant enough to invalidate the data collected from this site.

The overall assessment of DSI inspections did not reveal any significant deficiencies or discrepancies that would invalidate the data submitted in support of this study. According to DSI review, in general the data generated from the above sites inspected appear acceptable. However, DSI further notes that should the review of the pending two EIRs reveal new information that would impact the integrity of the data from the two foreign sites, they will amend this review and will notify the Review Division.

III. Human Pharmacokinetics and Pharmacodynamics

The sponsor previously submitted three clinical pharmacokinetic studies (066-087, AZM-NY-90-011, and AZM-F-93-004) comparing the 5-day regimen (500 mg on day 1, then 250 mg/day for days 2-5) to the 3-day regimen (500 mg/day for 3 days) of azithromycin in adults. These studies were submitted to support the pediatric efficacy supplements SE-008, SE-009, SE-010 for NDA 50-710 on 2/16/01. The results demonstrated that the total exposure ($AUC_{0-\infty}$) was similar between the 5-day and 3-day regimens. Since it is thought that the pharmacodynamic parameter most predictive of azithromycin efficacy based on *in vitro* and animal models is the AUC/MIC ratio, the 5-day and 3-day regimens may have similar clinical efficacy. Based on the similarity of the *in vitro* dissolution profiles, the dissolution characteristics of azithromycin 500 mg tablets are similar to 250 mg tablets and supports granting a waiver of in vivo bioequivalence studies to the applicant.

IV. Description of Clinical Data and Sources

A. Overall Data

The efficacy and safety data of study A01661013 in support for this New Drug Application (50784), in the treatment of acute bacterial exacerbation of chronic bronchitis were acceptable. A total of 404 subjects was randomized and treated in this study; however after removing the subjects from the study sites of [redacted], [redacted] the total evaluable subjects for efficacy were 306 (149 in the azithromycin treatment group and 157 in the clarithromycin treatment group). The safety data included all subjects randomized and who received at least one dose of the study medication. The safety data in the integrated summary of safety included selected adult clinical studies (Phase 1-4) conducted in foreign countries using the adult 3-day dosing regimen of azithromycin.

B. Tables Listing the Clinical Trials

There is only one pivotal study (A00661013) submitted for NDA 50784 in support for the claim of acute exacerbation of chronic bronchitis (AECB).

The table below lists the adult pivotal studies and legacy studies which provided safety information in the integrated summary of safety. (Note: Pediatric studies are excluded from this table.)

Table 1: List of Clinical Trials

Adult Studies	Indication	Study Design	Azithromycin/Comparator Dosing Regimen
Pivotal Studies A06610131	AECB	Double-blind, randomized, multicenter, comparative	Azi 500mg qd x3 days/ Clarithromycin 500 mg qd x 10 days
AZM-NY-93-007		Open-label, comparative, multicenter	Azi 500 mg qd x 3 days/ Clarithromycin 250 mg BID x 10 days
Legacy Studies AZM-NY-89-016B		Open-label, multicenter, non-comparative	Azi 500 mg qd x 3days
AZM-NY-95-005		Open-label,randomized, comparative	Azi 500 mg qd x 3days/Clari 250 mg BID x10 days
AZM-NY-92-009	AECB	Double-blind,double-dummy, randomized, multicenter	Azi 500 mg qd x 3 days/Augmentin 625 mg TID X 10 days
AZM-NY-89-017	AECB	Open-label,randomized comparative (pilot study)	Azi 500 mg qd x 3-5.days/ Amoxicillin 500 TID x 7-10 days
AZM-F-93-001	AECB	Double-blind, comparative, Multicenter, parallel group	Azi 500mg qd x 3 days/ Amoxicillin 1 gm BID x 7 days
AZM-F-94-002	AECB	Single-blind, comparative, multicenter, parallel group	Azi 500 mg qd x 3 days/Amoxicillin 500 mg-clavulanic acid 125 mg 3 TIDx 7 days
AZM-F-92-002		Single-blind, comparative, multicenter	Azi 500 mg qd x 3 days/Penicillin 3 million U TID x 10 days
AZM-F-92-004		Double-blind of active Azi 3-day and 5-day regimen and 10-day regimen of Penicillin (single-blind), multicenter	Azi 500 mg qd x 3-day vs 5-day regimen /Penicillin V 1 million U TID x 10 days
AZM-F-94-001		Double-blind, randomized multicenter	Azi 500 mg qd x 3days/Amoxicillin 500 mg BID x 10 days
Legacy Studies 066-326	Lower Respiratory Tract Infections (LRTI)	Double-blind, multicenter, Comparative	Azi 500 mg qd x3 days/Amoxicillin 500 mg TID x 5 days
AZM-NY-90-003 (Swiss & non-Swiss)		Open-label,randomized, comparative, multicenter	Azi 500 mg qd x 3days/ Roxithromycin 150 mg BID x 10 days
AZM-NY-90-013		Open-label, multicenter	Azi 500 mg qd x 3 days/ Clari 250 mg BID x 10 days

AZM-NY-90-018A		Double-blind. comparative	Azi 500 mg qd x 3 days/Augmentin 625 mg TID x 7 days
AZM-NY-90-018B		Open-label, multicenter	Azi 500 mg qd x 3 days/Augmentin 625 mg TID x 10 days
AZM-NY-92-004		Double-dummy, randomized, multicenter	Azi 500 mg qd x 3 days/Augmentin 625 mg TID x 10 days
AZM-NY-92-019		Open-label, multicenter	Azi 500 mg qd x 3 days/Augmentin 375 mg TID x 10 days
AZM-NY-98-001		Open-label, comparative, Comparative	Azi 500 mg qd x 3 days/10 mg/kg suspension qd x3 days/Clari 250 mg BID x 10 days
AZM-NY-88-002	Upper Respiratory Tract Infections (URTI)	Open-label, multicenter, non-comparative	Azi 500 mg qd x 3 days
AZM-NY-90-014		Open-label, randomized	Azi 500 mg qd x 3 days/ Clari 250 mg BID x 10 days
AZM-NY-90-015A		Open-label, randomized, multicenter	Azi 500 mg qd x 3days/Amoxicillin 500 mg TID x 10 days
AZM-NY-92-005		Open-label, randomized, multicenter	Azi 500 mg qd x 3days/ Roxithromycin 150 mg BID x 10 days
AZM-NY-92-016		Open-label, multicenter	Azi 500 mg qd x 3days/Cefaclor 250 mg TID x 10 days

C. Postmarketing Experience

The original marketing license in the United States was based on clinical trials utilizing 1.5 grams in adults or 30-60 mg/kg in children administered over 5 days. A total dose of 1.5 grams of azithromycin in adults or 30-60 mg/kg in children administered over 3 days has been approved by regulatory bodies in 51 countries. In more than 50 countries, the same total dose is administered as a 3-day regimen. The regimen currently approved for these indications in the U.S. is 500 mg on day 1 and 250 mg on days 2- 4 (NDA-50-670, April 11, 1990), but throughout most of Europe the 3-day regimen has already been in use for approximately 10 years, and was more recently approved in Japan. Both the 3-day and the 5-day regimens deliver a total azithromycin dose of 1500 mg. Initial approval of the 3-day regimen in Europe was largely based on pharmacokinetics. According to applicant, safety has been monitored through post-marketing surveillance systems in Europe.

V. Clinical Review Methods

A. How the Review Was Conducted

The clinical review was initiated by examination of the submitted materials in both electronic and paper submissions. After the 45-day period of fileability, the reviewer recommended that this application is fileable. The contents of the clinical section of the NDA including the pivotal study for acute bacterial exacerbation of chronic bronchitis were reviewed and found to be acceptable. All other members of the review team including chemistry, statistical, biopharmaceutics, animal pharmacology/toxicology and microbiology accepted the fileability of this application. The medical reviewer proceeded with the initial review process by looking at the study protocol in correlation with FDA's Guidance for Industry document. All case report forms were reviewed. All efficacy data were analyzed in conjunction with the biostatisticians. Additional efficacy datasets were requested from the applicant to aid in the primary and secondary analyses. Safety data of the study including data from the adult integrated summary of safety were then reviewed and analyzed.

B. Overview of Materials Consulted in Review

The materials in this application consisted of electronic materials from the clinical (efficacy and safety), statistical, and microbiology study reports. In addition materials for the case report forms, integrated summary of efficacy, integrated summary of safety, minutes of Pre-NDA meetings with the sponsor, labeling history and proposed text for the label of azithromycin were also reviewed. Archival reviews of the original NDA (50-670) were consulted in the review of this application. Four-month safety update submitted in the subsequent months during the review period was also examined.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was consulted by the reviewing Division (DAIDP) to assess the validity of clinical data submitted for this application. DSI performed inspections in two local (United States) study sites and two foreign study sites. (Note: Please refer to Section II: Clinically Relevant Findings from DSI of this review.)

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The study was conducted in accordance with the accepted ethical standards. The investigator/institution obtained written, dated approval from the Independent Ethics Committee or Institutional Review Board prior to starting the study. Ethics review was in accordance with local laws and regulations governing research on new therapeutic agents in the country of conduct, and also with informed consent regulations and ICH-GCP Guidelines. The investigator or designee explained the benefits and risks of participating in the study to each subject, subject's legally acceptable representative or impartial witness and obtained written informed consent prior to study entry (i.e., before initiation of non-routine tests and administration of study drug). Pfizer Central Research contracted principal investigators to conduct the study under its direction and in accordance with the study protocol.

E. Evaluation of Financial Disclosure

There are two studies covered in the original NDA including Study AZM-NY-93-007 and Study A0661013 for the indication of acute exacerbation of chronic bronchitis (ABECB). Due to the close of study AZM-NY-93-007 before February 2, 1998, the applicant is not required to provide Financial Disclosure information for investigators in this study, as defined by 21 CFR 54.2 (b) or 54.2(f). According to the applicant's Financial Disclosure Cover Note, no investigators associated with this NDA received variable compensation for the conduct of their study nor did they possess a proprietary interest in Zithromax. The only study covered for financial disclosure information is Study A0661013 for the indication of acute bacterial exacerbation of chronic bronchitis.

According to applicant, each of the individuals listed as principal investigators/subinvestigators was sent the Financial Disclosure Information Request Form directly or through the principal investigator for their site. In addition, the applicant contacted the site by telephone and/or sent two separate follow-up letters to those individuals who did not return the Financial Disclosure Form. All investigators contacted were reminded to disclose financial information for Warner-Lambert Company now wholly-owned by Pfizer. Pfizer has examined its financial data regarding significant payments of other sorts made to investigators in this study and equity information as provided by the investigators, as defined in 21 CFR 54.2.

Using Form 3454, certification is provided for 379 of the 385 investigators indicating, 1) investigators had nothing to disclose, or 2) due diligence in collecting the information was applied. According to Pfizer's request for financial information by investigators, the response rate was 98%. According to the applicant, none of the 385 investigators either did not respond or were not reached by their due diligence effort. Only six of the 385 investigators for Study A0661013 had financial information to disclose.

The following three principal investigators and three subinvestigators in Study A0661013 who had financial information disclosed were as follows:

- Dr. Marcus J. Zervos (Site ID 5078) – Total subjects screened: 137; Total subjects randomized: 6

  Total amount of money received by this principal investigator was [redacted] The completed Form FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical), indicated that the amount received by the investigator covered the following expenses, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. The payment exceeds threshold amount of [redacted]

- [redacted] (Site ID 5170) – Total subjects screened: 0; Total subjects randomized: 0

  The following disclosed [redacted] held by this subinvestigator were as follows:

  [redacted] Form FDA 3455 was marked as a significant equity interest, defined in the 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

- Dr. Guy W. Amsden (Site ID 5094) – Total subjects screened: 49; Total subjects randomized: 4

  Total amount of money received by this principal investigator was [redacted] The completed Form FDA 3455 stated that the amount received by the investigator covered the following expenses, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. The payment exceeds threshold amount of [redacted]

- [redacted] (Site ID 5084) – Total subjects screened: 3; Total subjects randomized: 1

  The following disclosed [redacted] this subinvestigator

  [redacted] Form FDA 3455 was marked as a significant equity interest, as defined in the 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

- Dr. Melvin Morganroth (Site ID 5084) – Total subjects screened: 3; Total subjects randomized: 1

Total amount of money received by this principal investigator was [redacted] The completed Form FDA 3455 stated that the amount received by the investigator covered the following expenses, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. The payment exceeds threshold amount of [redacted]

- Dr. Joseph F. Plouffe, Jr. (site ID 5110) – Total subjects screened: 0; Total subjects randomized: 0

  Total amount of money received by this principal investigator was [redacted] The completed Form FDA 3455 stated that the amount received by the investigator covered the following expenses, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. The payment exceeds threshold amount of [redacted]

Conclusion:

Based on the review of the financial disclosure information on the six investigators in this study, the overall findings did not impact the results and data analysis of the study. The number of subjects randomized by the above investigators were small and did not significantly affect the overall efficacy and safety analysis of the study.

V. Review of Efficacy

A. Brief Conclusions of Study A0661013

This study was submitted by the applicant, NDA 50-784 for marketing approval of azithromycin 500 mg tablets for the treatment of acute bacterial exacerbation of chronic bronchitis. After review and analysis of the data, the reviewer concludes that the treatment of acute bacterial exacerbation of chronic bronchitis with azithromycin 500 mg per day for three days administered orally is equivalent in efficacy to treatment with clarithromycin 500 mg twice a day for ten days administered orally. The safety profile of the azithromycin treatment group and the clarithromycin treatment group are comparable with respect to the severity of the adverse events.

B. General Approach to the Efficacy Review

After examination and general review of the submitted materials electronically from the applicant, the reviewer proceeded with the initial review process. Some additional datasets

and tables, including statistical, subject listing with pathogen results for microbiology and laboratory test results were requested from the applicant. By way of validating the data from the applicant, the reviewer performed a random sample analysis of the data, in a blinded-manner, of case report forms in 80 subjects at the same time correlating the CRF entry data with the procedure in the study protocol. The initial results of the random samples review were given to the Biostatistics reviewer and the Medical Team Leader. In the subsequent review period, the reviewer decided to analyze and review all the case report forms in the study because of the findings that some subjects had additional follow-up visits after the Test-of cure (TOC) visit, if the assessment of the investigator was "improvement" at TOC. This procedure was allowed in the study protocol. The reviewer utilized the JMP program to gather all essential efficacy dataset variables for the review. In addition to the primary analysis of the efficacy data, the reviewer together with the biostatistics reviewer performed post-hoc sensitivity analyses of the clinical outcomes at TOC in subjects with ABECB signs and symptoms (pre-exacerbation and baseline periods).

C. Detailed Review of Efficacy

Study A0661013 was a randomized, double-blind, double-dummy, multicenter trial which compared azithromycin 500 mg daily for 3 days with clarithromycin 1 gram daily for 10 days for the treatment of acute bacterial exacerbation of chronic bronchitis. Male or female subjects between the ages of 35 and 75 years with ABECB entered this randomized, double-blind, comparative, multicenter study. They received either oral azithromycin 500 mg/day as a single daily dose for 3 days or oral clarithromycin 1000 mg/day divided as 500 mg morning and evening for 10 days. Subjects were followed for 21-24 days. There were no protocol amendments. Within the 48 hours prior to baseline, as a screening procedure, all subjects had a physical examination and provided a medical history. Subjects were enrolled in the study after satisfying the inclusion/exclusion criteria, including provision of the appropriate informed consent. Chest X-rays were obtained to exclude the presence of pneumonia. Freshly expectorated sputum samples were examined macroscopically and microscopically to determine suitability for culture. Adequate specimens were submitted for culture with Gram stains to an approved local laboratory. The Gram stains and any culture isolates from the local laboratories were sent to the central laboratory to verify adequacy of Gram stain and to confirm the identification of the bacteria. The central laboratory also conducted susceptibility testing on all respiratory pathogens using azithromycin and clarithromycin. Isolation of a baseline pathogen susceptible to azithromycin or clarithromycin was not required to continue in the study. Subjects were to be assigned screening identification numbers sequentially at entry. Baseline visit was designated Visit 1 which included collection of demographic information, medical history and physical examination.

Follow-up included visits to the site on day 10-12 (designated Visit 2, End of Therapy [EOT]) and day 21-24 (designated Visit 3, Test of Cure [TOC]). The clinical outcome at

TOC, which was based on the investigator assessment, was the primary endpoint.

I. Efficacy Evaluation

Subject Disposition

The following table summarizes the subject disposition by evaluation treatment groups per applicant's analysis:

Table 1: Subject Disposition According to Applicant

SUBJECTS	Azithromycin	CLARITHROMYCIN
Randomized to treatment	158	164
Received Treatment	158	164
Discontinued Study	15	16
Subjects at TOC visit		
Clinical MITT	149	157
Bacteriological MITT	56	56
Efficacy Analysis at TOC		
Clinical PP	140	145
Bacteriological PP	53	53
Safety Analysis	158	164

The next table is the disposition of subjects according to the reviewer's analysis.

Table 2: Subject Disposition According to MO's Analysis

Subjects	Azithromycin	Clarithromycin
Randomized to treatment	158	164
Received Treatment	200	204
Discontinued Study	15	16
Subjects at TOC visit		
Clinical MITT	147	157
Bacteriological MITT	56	56
Efficacy Analysis at TOC		
Clinical PP	138	145
Bacteriological PP	53	53
Safety Analysis	200	204

MO COMMENT: After review of all the CRFs in the study, the MO assessed a total of 304 evaluable subjects in the clinical MITT population at TOC; 147 subjects in the azithromycin treatment group and 157 subjects in the clarithromycin group. In the PP population, there were 138 subjects in the azithromycin treatment group and 145 subjects in the clarithromycin group. Two subjects (#159 and # 434) were considered by the reviewer as unevaluable from the MITT population because they did not have baseline characteristics for chronic bronchitis. The reviewer included all subjects who received at least one dose of the study drug (including subjects randomized in sites of [redacted] for the safety analysis, hence the numbers are different from applicant's number as indicated in the above table.

Efficacy Results

The following table summarizes the patient baseline demographics in the study according to the applicant:

Table 3: Demographic Characteristics

	Azithromycin Group			Clarithromycin Group		
	Male	**Female**	**TOTAL**	**Male**	**Female**	**TOTAL**
Number of Subjects	**99**	**59**	**158**	**101**	**63**	**164**
Age (years)						
<18	0	0	0	0	0	0
18-44	4	15	19	15	14	29
45-64	54	24	78	52	41	93
>=65	41	20	61	34	8	42
Mean	61.4	55.5	59.2	57.9	53.6	56.2
SD	9.8	14.2	11.9	11.5	11.1	11.5
Range	33-82	31-81	31-82	30-76	33-91	30-91
Race						
White	72	41	113	72	46	118
Black	3	2	5	4	2	6
Asian	12	6	18	11	5	16
Other	12	10	22	14	10	24
Weight (kg)						
Mean	73.6	67.4		76.1	66.5	
SD	18.6	20.0		17.7	17.4	
Range	34-134	32-124		43-133	36-143	
N	99	59		100	63	
Height (cm)						
Mean	169.2	158.0		171.2	158.9	
SD	9.5	9.0		11.0	7.6	
Range	145-196	135-180		147-239	140-175	
N	99	59		101	63	
Smoking History						
Never Smoke	11	21	32	7	21	28
Ex-smoker	58	17	75	58	14	72
Smoker	30	21	51	36	28	64

MO COMMENT: The majority of the subjects were between 45 to 64 years old with a mean of 59.2 and a range of 31-82 years in the azithromycin treatment group, comparable to clarithromycin treatment group. Male and white patients were more prevalent in the study. Current and ex-smokers were predominant in both males and females. The applicant's table above was modified as to its format by the reviewer.

Primary Diagnosis

According to the applicant the primary diagnoses were the same for all 158 subjects receiving azithromycin and the 164 subjects assigned to clarithromycin, i.e., obstructive chronic bronchitis with acute exacerbation. Subjects in the azithromycin group had this diagnosis for a mean of 8.6 days with a range of 0 to 90 days. Subjects in the clarithromycin group had been diagnosed a mean of 7.9 days with a range of 0 to 56 days. The table below provides the number of subjects in the study with the primary diagnosis of obstructive chronic bronchitis with acute exacerbation.

Table 4: Primary Diagnosis and Duration According to Applicant

Primary Diagnosis - Obstructive chronic bronchitis with acute exacerbation	**Azithromycin**	**Clarithromycin**
Number of subjects screened	200	204
Duration Since First Diagnosis (days)		
Mean	8.6	7.9
Range	0.0-90.0	0.0-56.0
Unspecified	0	0

Past and present medical histories were similar for subjects in the two treatment groups. Within subjects assigned to azithromycin, 67% had at least one disease/syndrome in their past medical history and 99% had at least one disease/syndrome in their present medical histories. Past and present medical histories were positive for 66% and 100%, respectively, of the subjects receiving clarithromycin. Major categories of disorders noted, i.e., 20 or more subjects in either dosing group having the disorder in either past or present medical history, included arthropathies and related disorders, chronic obstructive pulmonary disease and allied conditions, disorders of the eye and adnexa, hypertensive disease, neurotic/personality/nonpsychotic mental disorders, operations on the digestive system, operations on the female genital organs, other diseases of the upper respiratory tract, other metabolic and immunity disorders, and pneumonia and influenza symptoms.

Summary of Baseline Signs and Symptoms

Each patient received a score of 0 to 3 (absent to severe) for each sign/symptom at each visit. The following table summarizes the mean signs and symptoms at baseline in the MITT population:

Table 5: Baseline Signs and Symptoms - MITT

	Pre-Exacerbation			Baseline		
	Cough	**Dyspnea**	**Sputum Production**	**Cough**	**Dyspnea**	**Sputum Production**
Azithromycin	0.98	0.84	0.95	2.32	1.98	2.41
Clarithromycin	0.94	0.80	0.90	2.26	1.96	2.33

MO COMMENT: As expected in this type of disease, the degree of severity of signs and symptoms (i.e., cough, dyspnea, and sputum production) during the exacerbation period are higher than the pre-exacerbation period. This is the case with the findings in this study.

The next table provides the baseline PFT values for clinical MITT subjects in the study.

Table 6: Baseline Pulmonary Function Tests (PFT) Values for Clinical MITT Subjects According to Applicant

PULMONARY FUNCTION TEST (PREDICTED VALUE)	AZITHROMYCIN	CLARITHROMYCIN
FEV1	61.1 %	61.9%
FVC	75.8%	77.2%
FEF (25-75)	42.4%	41.0%

MO COMMENT: The mean percents of predicted PFT values were very similar for the two treatment groups. The table by applicant has been modified as to its format by the reviewer.

Pulmonary function tests (PFT) were done at each visit, and values for FEV1, FVC, FEF (25-75), and PEFR were recorded. Means were computed for each treatment group at each visit.

Drug Administration

Subjects receiving azithromycin were treated a median duration of 3.0 days with a range of 1-3 days while subjects receiving clarithromycin were treated a median duration of 10.0 days with a

range of 1-12 days. The following table by the reviewer summarizes the duration of active treatment in the study:

Table 7: Duration of Treatment

NUMBER OF DAYS	AZITHROMYCIN 3-days	CLARITHROMYCIN 10-days
Days : 1	0	1
2	1	3
3	146	0
4	0	0
5	0	2
9	0	2
10	0	93
11	0	55
12	0	1
Median Duration	3	10
Range	1-3	1-12

MO COMMENT: The applicant defined duration category as the total number of days from first to and including last day of each active therapy. The median duration for the azithromycin treatment group was 3 days and 10 days for clarithromycin treatment group.

Concomitant Medications:

A total of 161 (80.5%) of the subjects receiving azithromycin and 164 (80.4%) of the subjects taking clarithromycin received concomitant medications. The next table summarizes the numbers of subjects taking concomitant medications under general categories during the study.

Table 8: General Categories of Medications Taken Concomitantly with Study Treatment by at least 10% of Subjects in both treatment groups according to Applicant:

Number of Subjects	AZITHROMYCIN	CLARITHROMYCIN
Analgesics	29 (14.5%)	41 (20.1%)
Antihypertensive Drugs	45 (22.5%)	31 (15.2%)
Bronchodilators	112 (56.0%)	116 (56.9%)