CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-809

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	50-809
Submission Code	000
Letter Date	July 29, 2005
Stamp Date	August 02, 2005
PDUFA Goal Date	June 02, 2006
Reviewer Name	Nasim Moledina, M.D.
Review Completion Date	May 30, 2006
Established Name	Azithromycin Citrate for Injection
(Proposed) Trade Name	N/A
Therapeutic Class	Azalide
Applicant	Sicor Pharmaceuticals, Inc.
Priority Designation	S
Formulation	500 mg/vial and 2.5 g/vial
Dosing Regimen	500 mg once a day
Indication	Community-acquired pneumonia and Pelvic Inflammatory Disease
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This NDA application is recommended approvable (AE) from CMC view point due to the

Based on FDA's previous findings of safety and efficacy of azithromycin for injection, the following recommendations are made by the Medical Officer:

Azithromycin for injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae*, or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Given prior experience with azithromycin products, no special risk management activity is required.

1.2.2 Required Phase 4 Commitments

N/A – The recommended action is to issue an approvable letter. At the time of approval, it is expected that there will be post-marketing commitments to perform pediatric studies.

1.2.3 Other Phase 4 Requests

N/A – **The recommended action** is to issue an approvable letter.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This NDA was filed as a 505(b)(2) application, so in accordance with CFR 314.54(a)(1)(iii), the sponsor has identified **Pfizer's Zithromax®** (azithromycin for injection) as the previously approved drug under NDA 50-733 for which FDA has made a finding of safety and effectiveness.

1.3.2 Efficacy

No additional data submitted.

1.3.3 Safety

No additional data submitted.

1.3.4 Dosing Regimen and Administration

Intravenous azithromycin 500 mg per day for 2 days followed by single daily oral dose of 500 mg to complete a 7-10 day course for CAP indication. The recommended dose for patients with PID is 500 mg as a single daily i.v. dose for one or two days followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7-day course.

1.3.5 Drug-Drug Interactions

No new studies submitted.

1.3.6 Special Populations

No new studies submitted.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The drug product is a lyophilized powder for injection containing 500 mg of azithromycin. The initial solution of azithromycin is reconstituted with 4.8 mL of sterile water for injection to the 500 mg vial. A pharmacy bulk of 2.5 gm azithromycin per vial is also proposed. The pharmacy bulk is reconstituted with 23 mL of sterile water for injection. The reconstituted solution is stable for 24 hours when stored below 30°C or 86°F. This solution should be inspected visually for particulate matters prior to administration. This solution is diluted in several media prior to administration. The dilution to a concentration range of 1.0-2.0 mg/mL in Normal saline, 5% **Dextrose in water, Lactated Ringer's Solution** and several other media are described in detail in the Package insert.

2.2 Currently Available Treatment for Indications

There are multiple antimicrobials of several classes approved for treatment of CAP and PID, including previously approved formulations of azithromycin.

2.3 Availability of Proposed Active Ingredient in the United States

Azithromycin is currently available in immediate release formulations administered orally by capsule, tablet, sachet, and powder or oral suspension, and in an intravenous formulation.

2.4 Important Issues With Pharmacologically Related Products

Several formulations of azithromycin have been approved in the USA. The current package insert for azithromycin I.V. product addresses all the issues with azithromycin and macrolide products.

2.5 Presubmission Regulatory Activity

The sponsor received a letter from FDA dated 30 August 2004 which confirmed that their proposed drug product qualified for a 505(b) (2) application.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

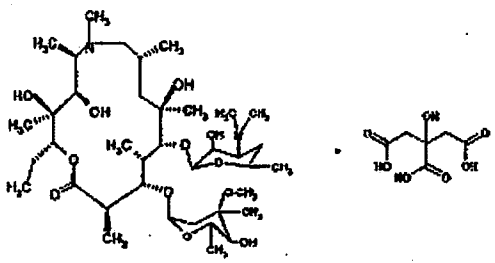
3.1 CMC (and Product Microbiology, if Applicable)

A detailed review of the CMC has been done by Dr. Andrew Yu. A brief summary of his review is as follows:

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

(*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-hepta-methyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Molecular weight 941.13
Formula $C_{44}H_{80}N_2O_{19}$



The drug substance was provided by the DMF holder.

This NDA application is recommended approvable (AE) from CMC view point due to

The drug substance manufacturing site was found acceptable by the Office of Compliance based on profile. The product manufacturing site was inspected and acceptable. Sicor did not claim EA exemption or a full EA package in the NDA. Instead, Sicor presented EA information on 50-733 (Azithromycin Intravenous injection from Pfizer) apparently obtained through FOI. The sponsor did not respond to this deficiency/IR comments.
A consolidated list of all deficiencies and comments can be found in Dr. Andrew Yu's review.

4.1 Animal Pharmacology/Toxicology

Reference is made to the approved NDA 50-733, azithromycin for injection. No new pharmacology/toxicology data were submitted to support the new formulation of azithromycin.

5 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

This section of the review is blank because no clinical data were provided in this NDA.

5.1 Sources of Clinical Data

5.2 Tables of Clinical Studies

5.3 Review Strategy

5.4 Data Quality and Integrity

5.5 Compliance with Good Clinical Practices

5.6 Financial Disclosures

6 CLINICAL PHARMACOLOGY

Refer to the detailed review by Jeffrey J. Tworzyanski, Pharm.D. A brief summary is presented here:

Since the proposed product is for intravenous use only and contains the same active moiety and inactive ingredients as the Reference Listed Drug, Zithromax, the FDA is willing to accept a comparison of the composition of the two products in lieu of an in vivo bioavailability/bioequivalence study and waive the requirement of performing an in vivo bioavailability/bioequivalence study as per 21 CFR 320.22(b)(1)(i).

6.1 Pharmacokinetics

Label information on pharmacokinetics **is based on publicly available information for Pfizer's** Zithromax® (azithromycin for injection).

6.2 Pharmacodynamics

N/A

6.3 Exposure-Response Relationships

N/A

7 INTEGRATED REVIEW OF EFFICACY

No new efficacy data submitted for this NDA. This NDA was filed as a 505(b)(2) application, so in accordance with CFR 314.54(a)(1)(iii), the sponsor **has identified Pfizer's Zithromax®** (azithromycin for injection) as the previously approved drug under NDA 50-733 for which FDA has made a finding of safety and effectiveness.
Proposed product labeling for this NDA is based on approved labeling for Zithromax® (azithromycin for injection).
The remainder of this section of the review is blank because no clinical data were provided in this submission.

7.1 Indication

7.1.1 Methods

7.1.2 General Discussion of Endpoints

7.1.3 Study Design

7.1.4 Efficacy Findings

7.1.5 Clinical Microbiology

7.1.6 Efficacy Conclusions

8 INTEGRATED REVIEW OF SAFETY

No new safety data submitted for this NDA. This NDA was filed as a 505(b)(2) application, so in accordance with CFR 314.54(a)(1)(iii), the sponsor has identified Pfizer's Zithromax® (azithromycin for injection) as the previously approved drug under NDA 50-733 for which FDA has made a finding of safety and effectiveness.
Proposed product labeling for this NDA is based on approved labeling for Zithromax® (azithromycin for injection).
The remainder of this section of the review is blank because no clinical data were provided in this submission.

8.1 Methods and Findings

8.1.1 Deaths

8.1.2 Other Serious Adverse Events

8.1.3 Dropouts and Other Significant Adverse Events

8.1.3.1 Overall profile of dropouts

8.1.3.2 Adverse events associated with dropouts

8.1.3.3 Other significant adverse events

8.1.4 Other Search Strategies

8.1.5 Common Adverse Events

8.1.5.1 Eliciting adverse events data in the development program

8.1.5.2 Appropriateness of adverse event categorization and preferred terms

8.1.5.3 Incidence of common adverse events

8.1.5.4 Common adverse event tables

8.1.5.5 Identifying common and drug-related adverse events

8.1.5.6 Additional analyses and explorations

8.1.6 Less Common Adverse Events

8.1.7 Laboratory Findings

8.1.7.1 Overview of laboratory testing in the development program

8.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

8.1.7.3 Standard analyses and explorations of laboratory data

8.1.7.3.1 Analyses focused on measures of central tendency

8.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

8.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

8.1.7.4 Additional analyses and explorations

8.1.7.5 Special assessments

8.1.8 Vital Signs

8.1.8.1 Overview of vital signs testing in the development program

8.1.8.2 Selection of studies and analyses for overall drug-control comparisons

8.1.8.3 Standard analyses and explorations of vital signs data

8.1.8.3.1 Analyses focused on measures of central tendencies

8.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

8.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

8.1.8.4 Additional analyses and explorations

8.1.9 Electrocardiograms (ECGs)

8.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

8.1.9.2 Selection of studies and analyses for overall drug-control comparisons

8.1.9.3 Standard analyses and explorations of ECG data

8.1.9.3.1 Analyses focused on measures of central tendency

8.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

8.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

8.1.9.4 Additional analyses and explorations

8.1.10 Immunogenicity

8.1.11 Human Carcinogenicity

8.1.12 Special Safety Studies

8.1.13 Withdrawal Phenomena and/or Abuse Potential

8.1.14 Human Reproduction and Pregnancy Data

8.1.15 Assessment of Effect on Growth

8.1.16 Overdose Experience

8.1.17 Postmarketing Experience

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

8.2.1.1 Study type and design/patient enumeration

8.2.1.2 Demographics

8.2.1.3 Extent of exposure (dose/duration)

8.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

8.2.2.1 Other studies

8.2.2.2 Postmarketing experience

8.2.2.3 Literature

8.2.3 Adequacy of Overall Clinical Experience

8.2.4 Adequacy of Special Animal and/or In Vitro Testing

8.2.5 Adequacy of Routine Clinical Testing

8.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

8.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

8.2.8 Assessment of Quality and Completeness of Data

8.2.9 Additional Submissions, Including Safety Update

8.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

8.4 General Methodology

8.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

8.4.1.1 Pooled data vs. individual study data

8.4.1.2 Combining data

8.4.2 Explorations for Predictive Factors

8.4.2.1 Explorations for dose dependency for adverse findings

8.4.2.2 Explorations for time dependency for adverse findings

8.4.2.3 Explorations for drug-demographic interactions

8.4.2.4 Explorations for drug-disease interactions

8.4.2.5 Explorations for drug-drug interactions

8.4.3 Causality Determination

9 ADDITIONAL CLINICAL ISSUES

9.1 Dosing Regimen and Administration

The recommended Dosing Regimen and Administration is based on approved labeling for **Pfizer's Zithromax®** (azithromycin for injection).

9.2 Drug-Drug Interactions

No new clinical data on drug-drug interactions were provided.

9.3 Special Populations

No new clinical data on use in special populations were provided.

9.4 Pediatrics

Pursuant to the Pediatric Research Equity Act, the sponsor amended their application to provide the proposal for the Pediatric Clinical Program. The proposed plan was received on May 8, 2006. The proposal describes the clinical development plans necessary to assess the safety and efficacy

of azithromycin for injection in pediatric patients for the labeled indications, Community Acquired Pneumonia and Pelvic Inflammatory Disease. The proposed pediatric clinical program is still under review at the time of this approvable action.

9.5 Advisory Committee Meeting

There are no plans for an advisory committee meeting.

9.6 Literature Review

None performed.

9.7 Postmarketing Risk Management Plan

None

9.8 Other Relevant Materials

N/A

10 OVERALL ASSESSMENT

10.1 Conclusions

Though no new clinical data has been submitted for review in this NDA, this NDA was filed as a 505(b)(2) application, so in accordance with CFR 314.54(a)(1)(iii), the sponsor has identified **Pfizer's Zithromax®** (azithromycin for injection) as the previously approved drug under NDA 50-733 for which FDA has made a finding of safety and effectiveness.

10.2 Recommendation on Regulatory Action

This NDA application is recommended approvable (AE) from CMC view point due to the [ ] The final approval of this product is pending till all the chemistry deficiencies have been addressed by the sponsor.

10.3 Recommendation on Postmarketing Actions

None at this time.

10.3.1 Risk Management Activity

Given prior experience with azithromycin products, no special risk management activity is required.

10.3.2 Required Phase 4 Commitments

N/A - The recommended action is to issue an approvable letter. At the time of approval, it is expected that there will be post-marketing commitments to perform pediatric studies.

10.3.3 Other Phase 4 Requests

N/A – The recommended action is to issue an approvable letter.

10.4 Labeling Review

The proposed heading of the package insert is as follows:

10.5 Comments to Applicant

The following recommendations made by the reviewers should be sent to the sponsor in a letter:

This NDA application is recommended approvable (AE) from CMC view point due to the

Based on the FDA's previous findings for safety and efficacy of azithromycin for injection, the following recommendations are made by the Medical Officer:

Azithromycin for injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae*, or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin.

APPEARS THIS WAY ON ORIGINAL

11 APPENDICES

11.1 Review of Individual Study Reports

No reports to review.

11.2 Line-by-Line Labeling Review

The proposed labeling for this NDA is based on approved labeling for **Pfizer's Zithromax®** (azithromycin for injection).

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REFERENCES

None

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/s/

Nasim Moledina
6/2/2006 11:28:47 AM
MEDICAL OFFICER

Final MOR for SICOR's Azithromycin citrate for injection

John Alexander
6/2/2006 02:54:10 PM
MEDICAL OFFICER

MEDICAL OFFICER'S MEMORANDUM TO FILE
NDA 50-809

Date: December 12, 2006

Applicant: Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618

Drug: Azithromycin Citrate for Injection

Background:

A new drug application (NDA) dated July 29, 2006, received August 2, 2006, was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Azithromycin Citrate for Injection 500 mg/vial and 2.5g/vial.
The applicant was advised to provide draft labeling in concurrence with comments expressed in the Advise Letter issued June 2, 2006.
An amendment to the NDA was submitted to FDA on June 16, 2006 which included the draft labeling.

Medical Officer's Review:

Based on the Medical Officer's Review signed off on June 2, 2006, all the comments on the proposed labeling (Refer to section 10.4 of the review) have been addressed in the draft label submitted in this amendment.

Medical Officer's Recommendations:

The labeling is acceptable. Please refer to the Dr. Andrew Yu's (chemistry reviewer) comments for further recommendations on the draft labeling.

Addendum (12/18/06)

The proposed labeling included

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/s/

Nasim Moledina
1/2/2007 09:52:53 AM
MEDICAL OFFICER

The revised memo to file for NDA 50-809

John Alexander
1/4/2007 10:30:36 AM
MEDICAL OFFICER