

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-784 / S-004, S-006

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



Food and Drug Administration
Rockville, MD 20857

NDA 50-784

Pfizer Inc.
Attention: Rita A. Wittich
Vice President, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Wittich:

Please refer to the telecon between representatives of your firm and FDA on October 31, 2002. The purpose of the telecon was to reach agreement on the proposed structure and content of a supplemental NDA (sNDA) for the treatment of acute bacterial sinusitis.

The official minutes of that telecon are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the telecon outcomes.

If you have any questions, call me at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Regulatory Project Manager
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Minutes of the telecon

MINUTES OF THE TELECON

MEETING DATE: October 31, 2002

TIME: 2:00-2:30 p.m.

LOCATION: Teleconference

APPLICATION: NDA 50-784, Zithromax 500 mg Tablets

TYPE OF MEETING: Pre-NDA, Efficacy Supplement

MEETING CHAIR: John Alexander, M.D., M.P.H., Medical Team Leader

FDA ATTENDEES, TITLES, AND DIVISION

Janice M. Soreth, M.D., Director, Division of Anti-Infective Drug Products
John Alexander, M.D., M.P.H., Medical Team Leader
Nasim Moledina, M.D., Medical Officer
Harold Silver, Microbiologist
Albert Sheldon, Ph.D., Microbiology Team Leader
Thamban Valappil, Ph.D., Biostatistics Reviewer
Daphne Lin, Ph.D., Biostatistics Team Leader
Judith Milstein, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Ann Carey, Director, Regulatory Affairs
Charles Knirsch, M.D., MPH Medical Director/Team Leader
Arlene Reisman, MPH, Director, Clinical Data Operations
Robert Swanson, M.D., Medical Director
Ronald Trust, Ph.D., Senior Associate Director, Regulatory Affairs, PGRD

BACKGROUND:

NDA 50-784 for Zithromax 500 mg Tablets was approved on May 24, 2002, for a 3-day dosing regimen to treat acute bacterial exacerbations of chronic obstructive pulmonary disease (COPD). Pfizer has completed studies for Zithromax 500 mg tablets (500mg/day for 3 days or 500 mg/day for 6 days) for the treatment of acute bacterial sinusitis due to *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Moraxella catarrhalis*.

Pfizer plans to submit a supplemental NDA (sNDA) for the new indication of acute bacterial sinusitis at the end of the first quarter of 2003.

MEETING OBJECTIVES:

To reach agreement on the proposed structure and content of the sNDA.

SUMMARY OF UNDERSTANDINGS

1. The summary data contained in the Information Package submitted September 27, 2002, contains adequate information to file an sNDA for the indication of acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*, with a proposed dosing regimen of 500 mg once daily for 3 day. Review of the sNDA will determine the adequacy of the submitted data in support of the new proposed indication.
2. A 4-month safety update will not be necessary, since there are not any ongoing studies of this formulation for this indication. However, if the sponsor identifies safety concerns from other indications or studies, the Division expects to be contacted and may request a safety update.
3. Pfizer's proposal to provide CRFs only for deaths and discontinuations due to adverse events (all causality) in the non-pivotal clinical studies is acceptable. Pfizer agreed to provide the Division with additional CRFs if their review becomes necessary.

QUESTIONS AND ANSWERS

After introductions, the questions posted by the sponsor (**bolded text**) in the briefing package submitted on September 27, 2002, were addressed as follows:

Question 1

The Information Package contains a summary of the data that will be available to support Pfizer's proposed indication and dosing regimen for the treatment of acute bacterial sinusitis in adults. Does the Agency have any specific concerns regarding the proposed indication of acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae* and the proposed dosing regimen of 500 mg once daily for 3 days?

The Division does not have any concerns regarding the filing of a sNDA for acute bacterial sinusitis. Review of the sNDA will determine the adequacy of the submitted data in support of the new proposed indication.

Question 2

Does the Agency concur with Pfizer's proposal to include the 6-day data in the Clinical Studies section of the package insert label?

Review of the data will determine what information will be included in the package insert. The Division also indicated that unless there is a clear advantage for the use the 6-day regimen instead of a 3-day regimen, or if a safety concern justifies the use of this 6-day regimen, the Division has always recommended the use of the shorter duration treatment. Normally, the Division has not added information in the package insert for longer regimens when a short regimen has been approved.

The Division also indicated the possibility of labeling the product as "use for 3-6 days". However, in order to incorporate this claim in the label, the data submitted in the sNDA needs to substantiate this claim.

Question 3

Is Pfizer's plan to file the sinusitis indication as a supplemental NDA to the Zithromax 500 mg Tablet NDA, approved for 3-day therapy for acute bacterial exacerbations of chronic obstructive pulmonary disease, acceptable?

The Division concurs with Pfizer's plan.

Question 4

Does the Division have any specific comments on the statistical analysis plans for the two pivotal clinical studies, A0661036 and A0661057?

The Division doesn't have any specific comments on the proposed statistical analyses.

Question 5

Does the Division have any concerns regarding the proposed content and structure of the Overall Summaries of Efficacy and Safety?

The overall summary of safety for this submission will only include the safety information gathered from the sinusitis studies. Safety information obtained from the 3-day treatment in AECB patients will be provided as the Post-Marketing data. The Division concurs with this approach.

Question 6

Does the Division agree with Pfizer's proposal for addressing the legacy 5-day and international study data?

The Division concurs with Pfizer's proposal for addressing the legacy 5-day and international study data.

Question 7

Regarding the non-pivotal clinical studies, is Pfizer's proposal to provide CRFs only for deaths and discontinuations due to adverse events (all causality) acceptable?

This proposal is acceptable. Pfizer agreed to provide the Division with additional CRFs if their review becomes necessary.

Question 8

Does the Agency concur with Pfizer's proposal that a 4-month safety update will not be necessary?

The Division concurs with Pfizer's proposal, considering that all the sinusitis studies are complete. However, if safety concerns arise from the review of other indications or studies, Pfizer would provide a safety update. If the Division identifies safety concerns from the review of the supplement, additional information may be requested.

Question 9

Does the Division have any specific comments regarding the following proposal for addressing the Pediatric Rule requirements?

We will seek a partial waiver from performing pediatric assessments in children less than 6 months old.

We plan to file a label claim for treatment of acute bacterial sinusitis in children 6 months of age and older based on the efficacy data in adults, the existing pharmacokinetic data, and the well-established safety profile of azithromycin in the pediatric population.

A court decision on October 17, 2002, has barred the FDA from enforcing the Pediatric Rule. However, if the Pediatric Rule remained in effect and/or were upheld, the Division would grant a partial waiver from performing pediatric assessments in children less than 6 months old. For children 6 months of age and older, the Division concurs with Pfizer that the efficacy of Zithromax in adults, the existing pharmacokinetic data, and the well-established safety profile in the pediatric population constitutes adequate data to file a label claim for the treatment of pediatric patients with acute bacterial sinusitis.

Question 10

Does the Division have any specific comments on the proposed Table of Contents for the sNDA?

The Division has no specific comments on the proposed Table of Contents for this sNDA.

Additional comments:

The Clinical Microbiology reviewer provided the following comments.

1. Under "Appendix E: Microbiological Methods", provide a complete description and results under the heading and sub-heading for each targeted microorganism.
2. Provide "Clinical Microbiology Line Listing" data in a similar (MITT Population) format as you did for the approved AECB indication.

Judit Milstein, Regulatory Project Manager, 11-1-02
John Alexander, M.D., M.P.H., 11-9-02

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Judith Milstein

3/25/03 04:39:04 PM

NDA 50-784/October 31, 2002 meeting minutes

John Alexander

3/26/03 03:21:16 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

VA# : 50-784

Supplement Type (e.g. SE5): SE6

Supplement Number: 004

Stamp Date: March 17, 2003

Action Date: January 15, 2004

HFD- 520 Trade and generic names/dosage form: Zithromax (azithromycin) Tablets, 500 mg

Applicant: Pfizer, Inc.

Therapeutic Class: 4010400 (macrolides)

Indication(s) previously approved: Acute Bacterial Exacerbations of Chronic Bronchitis (AECB)
Community-Acquired Pneumonia (CAP)
Pharyngitis/Tonsillitis (P/T)
Uncomplicated Skin and Skin Structure Infections (uSSSI)
Urethritis and Cervicitis
Genital Ulcer Disease

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1 (one)

Indication #1 : Acute Bacterial Sinusitis (ABS)

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: X Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min birth kg _____ mo. _____ yr. _____ Tanner Stage _____
Max 6 months kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population

- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min: 6 months kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max: 16 years kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments: Use of Zithromax for the treatment of Acute Bacterial Sinusitis in pediatric patients 6 months of age or greater is supported by adequate and well-controlled studies in adults, similar pathophysiology of acute sinusitis in adults and pediatric patients, and studies in acute otitis media in pediatric patients.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

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

/s/

Judit Milstein
1/30/04 12:53:52 PM
CSO