



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals
Attention: Helen K. Edelberg, MD, MPH
Associate Director, GDDC/US Regulatory Liaison
200 Crossing Boulevard
P. O. Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Edelberg:

Please refer to the meeting between representatives of your firm and FDA on December 19, 2002. The purpose of the meeting was to share with the Division the slides that Aventis will present at the upcoming Advisory Committee Meeting and discuss the agenda for the same meeting.

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

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

MEETING ATTENDEES

MEETING DATE: December 19, 2002

TIME: 1:00-4:00 p.m.

LOCATION: Corporate Building, Conference Room S300

APPLICATION: NDA 21-144/Ketek

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Mark J. Goldberger, M.D., MPH, Director, Office of Drug Evaluation IV
Janice M. Soreth, M.D., Director, Division of Anti-Infective Drug Products
John Alexander, M.D., MPH, Medical Team Leader
David Ross, M.D., Medical Team Leader
Chuck Cooper, M.D., Medical Officer
Alma Davidson, M.D., Medical Officer
Thomas Smith, M.D., Medical Officer
Janice Pohlman, M.D., Medical Officer
George Rochester, Ph.D., Statistician
Thamban Valappil, Ph.D., Statistician
Daphne Lin, Ph.D., Statistical Team Leader
Harold V. Silver, Microbiologist
Albert Sheldon Jr, Ph.D., Microbiology Team Leader
Jenny J. Zheng, Ph.D., Biopharmaceutics Reviewer
Philip Colangelo, Ph.D., Pharm.D., Biopharmaceutics Team Leader
Alfred Sorbello, M.D., Medical Officer
Peter Coderre, Ph.D., Microbiology Reviewer
Judit Milstein, Regulatory Project Manager
Wiley Chambers, M.D., Deputy Director, Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
Tara Turner, R.Ph., Advisory and Consultants Staff

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Larry Bell, M.D. - Senior Vice-President, Head, Worldwide Regulatory Affairs
Vijay Bhargava, Ph.D. - Senior Director, Head, Drug Metabolism and Pharmacokinetics
Steve Caffé, M.D. - Vice-President, Head, US Regulatory Affairs
Michael Goedde - Senior Manager, Data Management
Parvis Hamedani, M.D. - Vice-President, Head, Clinical Development for Anti-Infectives
Paul Lagarenne, M.D. - Vice-President, Head, Clinical Drug Safety
Bruno Leroy, M.D. - Senior Director, Global Project Team Leader
Roomi Nusrat, M.D. - Director, Global Clinical Development
John Pakulski, R.Ph. - Global Regulatory Affairs
Mark Quigley, Ph.D. - Vice-President, Head, Worldwide Quality Assurance
Sol Rajfer, M.D. - Senior Vice-President, Head, Worldwide Clinical Development
Divakar Sharma, Ph.D. - Director, Head of Biostatistics for Anti-Infectives
Kristen Sharma, M.D. - Director, Global Safety Officer

Michael Shoemaker - Senior Director, Global QA/GCP
Bill Stager, Ph.D. - Director, Biostatistics
Cathy Tropman, P.P.D.

BACKGROUND:

NDA 21-144, submitted February 28, 2000, received an approvable letter on June 1, 2001. A complete response to the approvable letter was submitted on July 24, 2001, and the submission is currently under review.

An Advisory Committee Meeting (AC) will be held on January 8, 2003.

In preparation for this Advisory Committee, Aventis Pharmaceuticals requested a meeting to share with the Division the slides for their presentation and discuss the agenda for the meeting.

MEETING OBJECTIVES:

1. To share with the Division the slides that Aventis will present at the upcoming AC.
2. To discuss the agenda for the meeting.

DISCUSSION:

Aventis indicated that they had reviewed the Division's briefing package for the upcoming AC and having identified some areas of disagreement, they would like to discuss them. These areas are related to the conduct of study #3014, information on the pharmacokinetics of telithromycin and post-marketing surveillance. The Division agreed to discuss these points, though they were not part of the meeting objectives.

The following comments pertain to Study # 3014.

Limitations to the design of Study # 3014 (e.g., detection of Adverse Events of Special Interest (AESIs), review of these AESIs by the CEC, definition of vasculitis and hepatic endpoints) were included in the FDA briefing package. The sponsor was concerned that these comments were overly critical of the study, though the review division felt the comments were balanced.

The Division is concerned about the integrity of the data for this study based on recent Division of Scientific Investigations (DSI) inspection. At the Division's request, Aventis described the monitoring process they used during the conduct of the study. They pointed to difficulties with follow-up on reported irregularities, considering the fast enrollment achieved during this trial. The following investigators were mentioned specifically:

Ann Kirkman Capmbell, M.D. (largest enroller)- DSI issued a 483 form to this investigator. Aventis indicated that when they became aware of irregularities at this site,

her participation was discontinued. The sponsor indicated that they did not identify other investigators with the same degree of irregularities as Dr. Kirkman-Campbell.

Egisto Salerno, M.D., (third largest enroller). Aventis indicated that a 483 form was issued to Dr. Salerno the same day of this meeting and that they were unaware that Dr. Salerno was on probation with the California Board of Medicine at the time the study was conducted.

The following comments pertain to the pharmacokinetics of telithromycin:

Aventis presented data that shows consistent 2-fold increase of the in PK parameters when telithromycin is co-administered with CYP3A4 inhibitors, other than with severely renally impaired patients. The Division agrees with this information, however is unsure on what constitutes a significant exposure. Both Aventis and the Division agreed to further discuss this issue at the time of labeling negotiations.

The following comments pertain to post-marketing reporting.

The Division is aware of numerous adverse event reports on visual disturbances reported from post-marketing surveillance in countries where Ketek is already approved. Even though these reports are consistent with the results of study # 3014, the Division is still concerned about the implications of these findings.

Aventis reported that considering that the actual number of prescriptions exceeds the 2 million, these reports do not constitute a significant proportion, and that no car crashes occurred due to the transient adverse event.

The following comments pertain to the Division concerns about AESI:

Visual: The visual adverse events could be explained as a difficulty in the accommodation mechanism for younger patients; however the Division is still trying to understand it in older patients where the accommodation ability is already lost. Current knowledge in the Agency indicates that there are some other drugs that temporarily delay this accommodation process (mostly ophthalmologic drug products) but this is the first drug that produces this extended difficulty in visual accommodation.

Hepatic: The cases of the patients with liver biopsy are not simple cases, and the Division is still evaluating these reports.

Cardiac: The Division is still reviewing the post-marketing report of Torsades de Pointes.

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this page is the manifestation of the electronic signature.**

/s/

Frances LeSane
4/23/03 04:12:15 PM

John Alexander
4/21/03 11:54:47 AM

