CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals Inc.
Attention: Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Caffé:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketek™ (telithromycin), Tablets, 400 mg.

We also refer to the approval letter issued on April 1, 2004, where the following errors where identified:

1. In page 10, **CLINICAL PHARMACOLOGY** section, **Other drug interactions** subsection, the paragraph describing the interaction with rifampin is in all capital letters. The correct paragraph should read:

   "**Rifampin:** During concomitant administration of rifampin and KETEK in repeated doses, C_{max} and AUC of telithromycin were decreased by 79% and 86%, respectively. (See **PRECAUTIONS, Drug Interactions.**)"

2. In page 17, **PRECAUTIONS** section, **Drug interactions** subsection, the paragraph describing the interaction with simvastatin is italicized. The correct paragraph should read:

   "In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**) Similarly, an interaction may occur with lovastatin and atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment."

3. In page 27, Patient Information the Rx only statement in the beginning of the document is unbolded and in all capital letters. It should be bolded to read:

"Rx only"

4. In page 28, **Patient Information, What about other medications I am taking,** subsection, the last bulleted statement is bolded. The correct bullet should read:

   "Medicines called diuretics (also sometimes called water pills) such as furosemide or hydrochlorothiazide."

5. In addition, approved versions for the bottle container label for the 60 tablets, the Ketek Pack carton, the Ketek Pack container, and the Ketek Pack tray were omitted.

You will receive a corrected action letter, where the action date will be unchanged; however the signature time will be one minute later to permit differentiation between the two letters.

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

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Lillian Gavrilovich
4/7/04 11:04:22 AM
Signing for Dr. Janice Soreth

100 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals Inc.
Attention: Helen K Edelberg, MD, MPH
Regulatory Liaison
200 Crossing Boulevard
P. O. Box 6890
Bridgewater, NJ 08807-0800

Dear Dr. Edelberg:

Please refer to the meeting between representatives of your firm and FDA on October 23, 2003. The purpose of the meeting was for Aventis to present the report entitled "Expert Statements on Telithromycin."

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 V. 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 MINUTES

MEETING DATE: October 23, 2003

TIME: 11:00 a.m.-12:30 p.m.

LOCATION: Corporate Building, Conference Room S-300

APPLICATION: NDA 21-144 (Ketek-telithromycin)

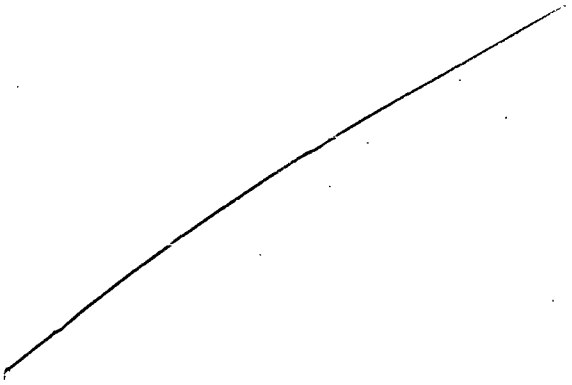
SPONSOR: Aventis Pharmaceuticals

TYPE OF MEETING: Guidance

MEETING CHAIR: Janice M. Soreth, MD

MEETING RECORDER: Judit Milstein

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:



Larry Bell, MD – Head, Worldwide Regulatory Affairs
Steve Caffé, MD – Head, US Regulatory Affairs
Frank Douglas, MD, PhD – Head, Drug Innovation and Approvals
Helen Edelberg, MD, MPH – US Regulatory Liaison
Lourdes Frau, MD – Head, Global Pharmacovigilance
Parviz Hamedani, MD – Head, Anti-Infective Clinical Development
Paul Lagarenne, MD – Head, Global Clinical Safety
Bruno Leroy, MD – Global Project Team Leader
Roomi Nusrat, MD – Global Clinical Development
Sol Rajfer, MD – Head, Worldwide Clinical Development
Barbara Rullo, MD – Therapeutic Area Head, Global Clinical Safety
Michelle Sumeray, PhD – Global Clinical Scientist

Via telephone

Center for Drug Evaluation and Research
Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV
Edward M. Cox, MD, Deputy Director, Office of Drug Evaluation IV
David Roeder, Associate Director for Regulatory Affairs, Office of Drug Evaluation IV
John Powers, MD, Medical Officer, Office of Drug Evaluation IV
Janice Soreth, MD, Director, Division of Anti-Infective Drug Products (DAIDP)
Lillian Gavrilovich, MD, Deputy Director, DAIDP
John Alexander, MD, MPH, Medical Team Leader, DAIDP
David Ross, MD, PhD, Medical Team Leader, DAIDP
Charles Cooper, MD, Medical Reviewer, DAIDP
Alma Davidson, MD, Medical Reviewer, DAIDP
Janice Pohlman, MD, Medical Reviewer, DAIDP
Thomas Smith, MD, Medical Reviewer, DAIDP
George Rochester, PhD, Safety Team Leader, Division of Biometrics III
Thamban Valappil, PhD, Statistical Reviewer, DAIDP
Daphne Lin, PhD, Statistical Team Leader, DAIDP
Harold Silver, Microbiology Reviewer, DAIDP
Albert Sheldon Jr., PhD, Microbiology Team Leader, DAIDP
Jenny Zheng, PhD, Clinical Pharmacology Reviewer, DAIDP
Robert Osterberg, PhD, Pharmacology and Toxicology Team Leader, DAIDP
Anitra Denson, MD, Staff Fellow, DAIDP
James D. Vidra, PhD, Chemistry Team Leader, DAIDP
Andrew Yu, PhD, Chemistry Reviewer
Judit Milstein, Regulatory Project Manager, DAIDP

BACKGROUND

NDA 21-144 received an approvable action on January 24, 2003.
During the meeting held on August 7, 2003, the sponsor requested a second meeting to discuss the Efficacy and Safety of Telithromycin.
Aventis provided a briefing package containing the "Expert Statements on Telithromycin" on September 24, 2003.

OBJECTIVE

The objective of this meeting was to allow Aventis the opportunity to bring in their group of experts to present their "Expert Statements on Telithromycin" report. These consultants prepared this document to address the concerns of the Division about the safety and efficacy of telithromycin.

DISCUSSION

Expert consultants from Aventis presented slides on the efficacy and safety of Ketek, and copy of these slides are attached to this document.

Highlights of the presentation and discussion on the efficacy of telithromycin included:

- Drug-resistance among Respiratory Tract pathogens, in particular macrolide-resistance in pneumococci.
- Telithromycin in the treatment of Acute Bacterial Sinusitis (ABS), Acute Exacerbation of Chronic Bronchitis (AECB), and Community-Acquired Pneumonia (CAP).
- The expert opinion as to the role of telithromycin in the treatment of Respiratory Tract Infections.
- Relevance of distinction between penicillin-resistant *S. pneumoniae* (PRSP) and macrolide-resistance *S. pneumoniae* (MRSP).
- Impact of MRSP in the outpatient setting.

Highlights of the presentation and discussion on the safety of telithromycin included:

- An overview of the safety data from the clinical trials performed by Aventis and the available post-marketing data.
- Particular adverse events (AEs) of interest, including cardiac and hepatic AEs.
- The identification of exacerbations of myasthenia gravis in post-marketing data.
- The available information on the mechanism and characteristics of the visual AE's.

AGREEMENTS

No conclusions or agreements were made as they were not the objectives for this meeting.

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/s/

Janice Soreth
11/21/03 04:46:55 PM

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 Liaision
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 August 7, 2003. The purpose of the meeting was

1. To discuss Aventis' approach to address the Post-Marketing safety data requested in the approvable action.
2. To discuss Aventis' approach to address question 1.A.1. of the approvable letter (related to Study # 3014).
3. To reach consensus on the timing for a meeting to present the "Expert report on Safety and Efficacy of Ketek"

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 MINUTES

MEETING DATE: July 7, 2003

TIME: 9:30-11:00 a.m.

LOCATION: Corporate Building, Conference Room S-200

APPLICATION: NDA 21-144, Ketek

SPONSOR: Aventis Pharmaceuticals, Inc.

TYPE OF MEETING: Guidance

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:
Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV
Edward Cox, MD, Deputy Director, Office of Drug Evaluation IV
David Roeder, ADRA, Office of Drug Evaluation IV
Janice M.Soreth, MD, Director, Division of Anti-Infective Drug Products
David Ross, MD, PhD, Medical Team Leader
John Alexander, MD, MPH, Medical Team Leader
Charles Cooper, MD, Medical Officer
Judit Milstein, Regulatory Project Manager
Brenda Friend, RPh, JD, Division of Scientific Investigations
Susmita Samanta, MD, Regulatory Project Manager
Ni Khin, MD, Medical Officer, Division of Scientific Investigations

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
Aventis Pharmaceuticals, Inc.

Name	Title
Bell, Larry	Head, Worldwide Regulatory Affairs
Caffé, Steve	Head, US Regulatory Affairs
Chaudhuri, Sharmila	Data Management
Douglas, Frank*	Executive Vice President; Head, Drug Innovation & Development
Edelberg, Helen	US Regulatory Liaison
Frau, Lourdes	Head, Global Pharmacovigilance and Epidemiology
Grethe, Nadine	Clinical Study Manager
Hamedani, Parviz	Head, Anti-Infective Clinical Development
Lagarenne, Paul	Head, Global Clinical Safety
Leroy, Bruno	Global Project Team Leader
Merat, Patrick	Vice President Global Clinical Operations
Mittnacht, Stewart	Head, Global and North American Submissions

Nusrat, Roomi	Global Clinical Development
Pakulski, John	Global Regulatory Coordinator
Quigley, Mark	Head, Global Quality Assurance
Richards, Owen	Quantic Regulatory Services LLC
Rajfer, Sol	Head, Worldwide Clinical Development
Shoemaker, Mike	Head, Global Clinical Quality Assurance
Sharma, Divikar	Head, Biostatistics, Anti-Infectives and Cardiovascular
Sharma, Kristen	Global Safety Officer

*Dr. Douglas participated by teleconference

BACKGROUND:

NDA 21-144, received an approvable action on January 24, 2003, for the indications of Community-Acquired Pneumonia (CAP), Acute Exacerbation of Chronic Bronchitis (AECB), and Acute Sinusitis (AS).

Submission dated May 22, 2003, contains Aventis' proposed approach to address the Post-Marketing safety data requested in the approvable action.

Submission dated June 2, 2003, contains a meeting request to discuss Aventis' proposed approach to address question 1.A.1. from the approvable letter (related to Study # 3014). The meeting was granted for July 24, 2003, and later rescheduled at the Division's request for August 7, 2003. The briefing package for this meeting was submitted in electronic format on July 3, 2003. The Division also agreed to discuss during this meeting Aventis' proposed approach to address the Post-Marketing safety data.

A teleconference was held on August 4, 2003, at Aventis' request, where Aventis provided a pre-meeting verbal update on additional potential non-serious adverse events (AEs) that were identified and were not reported in the Study #3014 database. The Division agreed to discuss these findings at the August 7, 2003 meeting.

On August 6, 2003, Aventis provided a revised meeting agenda that was followed for this meeting.

MEETING OBJECTIVES:

1. To discuss Aventis' approach to address the Post-Marketing safety data requested in the approvable action.
2. To discuss Aventis' approach to address question 1.A.1. of the approvable letter (related to Study # 3014).
3. To reach consensus on the timing for a meeting to present the "Expert report on Safety and Efficacy of Ketek"

SUMMARY OF UNDERSTANDINGS

1. A meeting will be scheduled for Aventis to present the "Expert report on Safety and Efficacy of Ketek."

2. The Division will provide a list of additional sites from which monitoring information would be necessary.

3. The Division will provide Aventis with comments on the proposal for the Post-Marketing safety data.

4. A meeting will be scheduled to provide hands-on demonstration on Amendment 3 resubmission.

DISCUSSION

Organization and navigation of Amendment 3

Aventis presented their proposal for organization and navigation of the requested documents related to Q1A1 of the action letter and AE case files for the postmarketing safety.

Aventis and the Division agreed to schedule a meeting to provide hands-on demonstration on Amendment 3 resubmission.

Proposed approach to Question 1.A.1. (Study # 3014)
Aventis described the AE document flow in Study 3014 and presented a timeline of AE errata (for those potential AEs not captured in the previous submission). AEs for this errata will be categorized as confirmed/unconfirmed.

Aventis commented on AE for patient 0495/006 (AESI for elevated ALT), and will submit this information to the NDA.

Aventis provided an update on Site 0083 (Investigator — . Aventis will notify DSI of these findings, and provide monitoring and auditing documents. The narratives on the 5 AESIs reported at this site will also be provided.

The Division requested a copy of Aventis' SOP relating to procedures for deciding what action to take if a site was poorly compliant with GCPs.

The Division will provide a list of additional sites whose monitoring information is to be included in Amendment 3.

Postmarketing Safety Data

The Division requested Aventis to provide all narratives, serious and non-serious, regardless of causality, for the post-marketing events. As for the Clinical Trials and information from the German Survey, it would be acceptable to exclude the non-serious narratives.

The Division will provide comments on the Proposed approach to the Post-marketing Safety Data.

Aventis presented a proposal for the submission of the Monthly Safety Update reports and 6-month bridging post-marketing safety data. The Division concurred with Aventis' proposal.

Expert report on safety and efficacy

Expert report contains a summary of the efficacy and safety of telithromycin and the clinical relevance of MRSP. A meeting will be scheduled for the presentation of this expert report.

ADDITIONAL COMMENTS

Between August 7, 2003, and the date of issuance of these minutes, the following steps were taken:

1. A meeting was scheduled for October 23, 2003, for the presentation on the "Expert Report on Safety and Efficacy of Telithromycin."

2. The list of additional sites from which monitoring information was needed was forwarded via e-mail on August 14, 2003.

3. Comments on the proposal for the Post-Marketing safety data were forwarded to the sponsor on August 7, 2003.

4. A hands-on demonstration on Amendment 3 resubmission was conducted on August 26, 2003.

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/s/

Frances LeSane
9/5/03 02:57:36 PM

David Ross
9/5/03 03:44:38 PM

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 Opthalmologic 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

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 Invetigations (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:
>
> _____, 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

, M.D.,(third largest enroller). Aventis indicated that a 483 form was issued to Dr. the same day of this meeting and that they were unaware that Dr. was on probation with the 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 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 opthamologic 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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/s/

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

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

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 February 28, 2003. The purpose of the meeting was to discuss Aventis' proposal to address the deficiencies listed in the approvable letter dated January 24, 2003.

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 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 meeting

MEETING MINUTES

MEETING DATE: February 28, 2003

TIME: 11:30 a.m.-1:00 p.m.

LOCATION: Corporate Building, Conference Room S-300

APPLICATION: NDA 21-144/Ketek (telithromycin)

TYPE OF MEETING: Guidance

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION
Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV (ODE IV)
Edward Cox, MD, Deputy Director, ODE IV
Janice Soreth, MD, Director, Division of Anti-Infective Drug Products
John Alexander, MD, MPH, Medical Team Leader
David Ross, MD, PhD, Medical Team Leader
Janice Pohlman, MD, Medical Officer
Thomas Smith, MD, Medical Officer
Alma Davidson, MD, Medical Officer
Charles Cooper, MD, Medical Officer (via telephone)
George Rochester, PhD, Statistician
Daphne Lin, PhD, Statistics Team Leader
Jenny Zheng, PhD Biopharmaceutics Reviewer
Philip Colangelo, PhD, Biopharmaceutics Team Leader
Harold Silver, Microbiologist
Albert Sheldon, PhD, Microbiolgy Team Leader
Terry Peters, DVM, Pharm/Tox Team Leader
Andy Yu, Chemistry Reviewer
David Roeder, Associate Director for Regulatory Affairs, OND III
Judit Milstein, Regulatory Project Manager
Brenda Friend, RPh, JD, Consumer Safety Officer, DSI
Ni Khin, MD, Medical Officer, DSI
Wiley Chambers, MD, Deputy Director, DAIAODP
Mohamed Huque, PhD, Director, Division of Biometrics III

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
Larry Bell, MD – Head, Worldwide Regulatory Affairs
Steve Caffe, MD – Head, US Regulatory Affairs
Sharmila Chaudhuri – Data Management
Helen Edelberg, MD, MPH - US Regulatory Liaison
Nadine Grethe – Global Clinical Operations
Parvis Hamedani, MD – Head, Global Clinical Development, Anti-Infective Drugs
Paul Lagarenne, MD – Head, Worldwide Pharmacovigilance
Bruno Leroy, MD – Global Project Leader
Roomi Nusrat, MD – Global Clinical Development
John Pakulski, RPh – US Regulatory Coordination
Mark Quigley, PhD – Head, Worldwide Quality Assurance

Sol Rajfer, MD – Head Worldwide Clinical Development
Kristen Sharma, MD – Pharmacovigilance
Divakar Sharma, PhD – Head, Biostatistics, Anti-Infectives
Michael Shoemaker, PhD – Head, Global Clinical QA
William Stager, PhD – Biostatistics

BACKGROUND

An approvable action was taken on Ketek on January 24, 2003. Terms of this letter included a request for additional data and analyses in the areas of safety, clinical pharmacology, and labeling.
Aventis requested a meeting to clarify the questions raised in the approvable letter (**bolded text** below) and to reach agreement on the approach to addressing these questions. A briefing package containing Aventis' proposal to address the deficiencies was submitted on February 18, 2003.
Aventis also requested comments on the proposed protocol designed to evaluate the implementation of the Monitoring Plan and Auditing Plan used for Study #3014 and to assess the impact of observed deviations on the validity of the Study #3014 safety data relating to adverse events of special interest (AESIs). The Division informed Aventis prior to the meeting that comments on this protocol would not be addressed at the February 28, 2003, considering the short time elapsed between submission of the protocol and timing of the meeting.

These minutes reflect the highlights of the discussion held at this meeting. Unless otherwise specified, the Division concurs with Aventis' proposed response to the deficiencies indicated in the action letter.

Q1A1

Study #3014 – "A Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin [Ketek] and Amoxicillin-Clavulanic Acid [Augmentin] in Outpatients with Respiratory Tract Infections in a Usual Care Setting".

1) In order to assess overall data integrity and to determine what role Study #3014 can have in support of your marketing application, you must provide the following information:

(a) A list of the sites at which Aventis and/or any contract research organization (CRO) conducted quality assurance audits or monitoring visits, the dates of these audits/visits, and copies of the findings. These should be sorted by site and arranged chronologically within each site. To assist in finding individual sites, the document should be indexed.

(b) Records of any communications between Aventis and any CRO regarding any irregularities.

(c) Information on any specific steps taken post-monitoring to address irregularities.

Aventis indicated that auditing of he conduct of study # 3014 did not show significant deviations from Good Clinical Practices (GCP), and that review of the issues addressed in the 483 forms for Dr. [redacted] Dr. [redacted] and Dr. [redacted] did not raise any concerns about the conduct of the study.

The Office of Drug Evaluation IV (ODEIV), and the Division consider the review of Aventis' monitoring plan in conjunction with [redacted] as supporting information and that review of all the data as requested in the action letter is necessary to evaluate the data integrity of study #3014. Review of this data will determine if additional sites will be inspected by the Division of Scientific Investigations (DSI).

The Division is aware of the volume of documents involved, and requested that the information on Drs [redacted] sites be submitted first. It was also suggested that [redacted] could review the monitoring derived from these sites, to be able to further understand the requirements and scope of their monitoring review. Review of this data will determine if information for additional sites will be requested.

The Division also indicated that proper conduct of a study must include among other components, enrollment of patients with the disease under study, administration of study medication as described in the protocol, follow-up and collection of protocol-specific clinical and laboratory data.

The Division indicated that the protocol proposed for the [redacted] monitoring plan lacks a definition of success and that an algorithm for what constitutes a significant deviation from the protocol needs to be explicitly defined. The Division will work with Aventis to refine the protocol.

Factors that the Division evaluates when deciding an inspection sites may include:

- Enrollment of patients without infections
- Patients returning for follow-up visits
- Missing laboratory data
- Enrollment of family or staff members
- Patients being followed up after report of adverse events (AEs)
- Sites with large number of patients relative to the total population of the area of enrollment
- Large sites with low number of AEs

If the integrity of the data for study #3014 cannot be assured, this study may not support the safety of telithromycin. In that case, the Division will have to rely on the data from post-marketing surveillance for the determination of the safety of the product and proposed labeling.

Q1A2

Submit analyses for Study #3014 pooling the following MedDRA preferred terms: Vision blurred, accommodation disorder, visual disturbance not otherwise specified (NOS), visual acuity reduced, vision abnormal NOS, visual hallucinations, diplopia, binocular eye movement disorder. In these pooled analyses, provide the following information: overall incidence rate regardless of attribution, rate of discontinuation, rate of serious adverse events, rate for men vs. women, and the relative frequency of mild, moderate and severe events. Present these analyses for both telithromycin and comparator.

Q1A3

Provide analyses for Study #3014 addressing the issue of onset and duration of visual AEs (including the following MedDRA preferred terms: Vision blurred, accommodation disorder, visual disturbance NOS, visual acuity reduced, vision abnormal NOS, visual hallucinations, diplopia, binocular eye movement disorder). With regard to duration of the AE, these analyses should be presented for two separate groups: those patients who continued the medication and those who discontinued. These analyses should describe the duration of symptoms in those patients who discontinued the drug as well as in those who continued the drug. Provide descriptive statistics (e.g., mean, median, range) of the time of onset of visual abnormalities after the start of treatment. Present these analyses in terms of hours, if possible, otherwise present them

in terms of days. Also, provide the number of visual AEs that began on each day of therapy. Provide an analysis of the duration of the pooled visual AEs by day of onset.

The following Division comments pertain to both Q1A2 and Q1A3

Include in the analysis ALL adverse events effecting vision. The complete list is as follows:

Vision Blurred
Visual Acuity Reduced
Diplopia
Hallucination, visual
Visual disturbance NOS
Vision Abnormal NOS
Asthenopia
Hallucination NOS
Accommodation disorder
Binocular eye movement disorder NOS
Chromatopsia

The following additional analyses of the visual events would be helpful in labeling this product.

Assess the duration of visual adverse events after the last dose of telithromycin. This analysis should include separately patients who discontinued telithromycin and those patients whose visual adverse events continued until completion of therapy.

Assess the rate of resolution on therapy of visual adverse events for those patients who continued telithromycin despite the visual adverse events.

Assess the time to resolution and severity of visual adverse events according to number of doses received.

Q1B1
Post-Marketing Data

1) **Data provided as narratives are incomplete. In order to better assess the post-marketing data, provide an accurate and complete English translation for original and follow-up Adverse Event (AE) reports for all post-marketing reports received as of January 31, 2003, in all countries where telithromycin has been approved. This submission should contain all original and follow-up post-marketing reports, without regard to causality. These reports should be indexed by manufacturer report number and provided as a separate bookmarked pdf file. This information should also be provided in the form of SAS transport files. These files should include line listings with all variables contained in the post-marketing SAS transport file dated December 13, 2002. Additionally, include any variables contained in the MedWatch form (Form 3500) not already contained in the SAS transport files. Provide a data dictionary defining all variables and possible variable responses.**

Provide narratives of all adverse events, not just the "serious, associated adverse events". Include a variable to relate these AEs to a specific country of origin.

Q1B3
Provide updated information on telithromycin exposure by country (including the source of these data) through January 31, 2003.

Aventis confirmed that the format and calculation method would be the same as the ones used in the Periodic Safety Update Report (PSUR).

Q1B4
In addition, while you are preparing a complete response to this letter and while the submission is under review, provide on a monthly basis all AE reports (as described above) and updated information on telithromycin exposure by country received after January 31, 2003.

Include in this report all new AEs, including clinical and follow-up cases. The report should also include the growing cumulative AEs by System Organ Class (SOC).

Q1B5
Provide a description of the amount of repeated use of telithromycin that has occurred in post-marketing use. Describe how the amount of repeated use was determined. Include any safety information available on patients who received repeated courses of telithromycin.

During the examination of AE profiles of specific events, include visual AEs, in addition to the proposed hepatic events, allergic reactions/hypersensitivity, and vasculitic events.

Q1B6
Submit the protocol for the intensified monitoring survey instituted in Germany (Study #5001; "An Open Observational Survey in Outpatients with Pharyngitis (> 12 years of age) or Mild to Moderate CAP, AECB or ABS (> 18 years of age)"). Provide in this submission a report of the findings.

Provide narratives of all adverse events, not just the "serious, associated adverse events".

Q1B2, Q1B7, Q1C1, Q1C2, Q2A, Q2B, Q3A1, A2, A3, Q3B-G

The Division concurs with Aventis proposal for these questions.

Judit Milstein, Regulatory Project Manager, March 21, 2003

David Ross, MD, PhD, Medical Team Leader concurrence, March 21, 2003

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
4/7/03 08:49:19 AM

David Ross
4/14/03 01:40:21 PM
2/28/03 Minutes of the meeting

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals Inc.
Attention: Paul Bryers, Ph.D.
US Regulatory Liaison
200 Crossing Boulevard
P. O. Box 6800
Bridgewater, NJ 08807-0890

Dear Dr. Bryers:

Please refer to the meeting between representatives of your firm and FDA on March 11, 2002. The purpose of the meeting was to discuss the customization of data sets, and content and format for the planned resubmission of Ketek™.

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

Enclosure: 1. Minutes of the meeting (content and format of the NDA)
2. Minutes of the meeting (customization of data sets)

SPONSOR MEETING ATTENDEES

Meeting Date: March 11, 2002 1:00-2:30 p.m.

Location: Corporate, Room S300

NDA/ Name: 21-144, Ketek (telithromycin)

Sponsor: Aventis Pharmaceuticals

Type of Meeting: pre-NDA, content and format of the NDA

Meeting Chair: John Alexander, M.D., Medical Team Leader
Division of Anti-Infective Drug Products

Aventis Pharmaceuticals	Title
Divakar Sharma	Global Biostatistics
Bill Stager, Ph.D.	Global Project Biostatistics
Steve Caffe, M.D.	Head, U.S. Regulatory Affairs
Tom Watson	U.S., Regulatory Affairs
Bruno Leroy, M.D.	Global Project Leader
Stephen Jenkins, Ph.D.	Global Head of Clinical Microbiology
Vijay Bhargava, Ph.D.	Clinical Pharmacology
Steward Mittnacht	Head, Global Submissions
Roomi Nusrat, M.D.	Global Clinical Director
Division of Anti-Infective Drug Products	
Janice Soreth, M.D.	Division Director
John Alexander, M.D.	Medical Team Leader
Charles Cooper, M.D.	Medical Officer
David Ross, M.D.	Medical Team Leader
Janice Pohlman, M.D.	Medical Officer
George Rochester, Ph.D.	Statistics Reviewer
Daphne Lin, Ph.D.	Statistics Team Leader
Harold Silver	Clinical Microbiology Reviewer
Albert T. Sheldon Jr., Ph.D.	Clinical Microbiology Team Leader
Kenneth Seethaler, Ph.D.	Pharmacology Reviewer
Terry Peters, D.V.M.	Pharmacology Team Leader
Jenny J. Zheng, Ph.D.	Clinical Pharmacology Reviewer
Sue-Chih Lee, Ph.D.	Clinical Pharmacology Acting Team Leader
Andrew Yu, PH.D.	Chemistry Reviewer
Raquel Peat	Project Manager
Judit Milstein	Project Manager

BACKGROUND:

NDA 21-144 was submitted February 28, 2000, with the following indications:
1. Community-Acquired Pneumonia (CAP),
2. Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB),
3. Acute Bacteria Sinusitis (ABS) and
4. Pharyngitis/Tonsillitis (PT).

A non-approvable action was taken on June 1, 2001 for the PT indication.

An approvable action was taken on June 1, 2001 for CAP, ABECB, and ABS indications. Deficiencies included potential risks posed by the concentration-related effect of telithromycin on cardiac repolarization, hepatotoxicity, and drug exposure in patients with renal/hepatic impairment.

In order to expedite the review of the resubmission (6-months review clock), the Division and Aventis agreed to hold discussions on the content and format for the planned resubmission, as well as the customization of data sets.

These minutes reflect the highlights of the discussions held regarding the content and format of the planned resubmission. Discussions during the meeting were based on the Division's fax dated March 6, 2002, and on the material included in Aventis' presentation entitled " Clinical Slides".

DISCUSSION:

SUMMARY OF UNDERSTANDINGS

1. Datasets for laboratory tests, with the most extreme value within each defined window, will be displayed.
2. Datased "clutter" will be reduced. Incomplete, redundant and unused variables will be removed unless they are used in the program.
3. An alphabetized master data set variable dictionary will be provided with format consistent with the example provided by FDA.
4. Patient profiles for all patients, including those in Study 3014 entitled " Randomized, Open-Label, Multicenter Trail of the Safety and Effectiveness of Oral Telithromycin (Ketek) Versus Amoxicillin/clavulanic acid (Augmentin) in Patients with Respiratory Tract Infections in Usual Care Settings" will be provided.
5. Case Report Forms (CRFs) will be provided for
   a. All Phase 3 studies. This will allow the Division to generate random samples for QC purposes.
   b. Patients who died.
   c. Patients who did not complete the study due to adverse events.
   d. Patients with serious adverse events.
   e. Only for Study 3014, patients with adverse events (AE's) of special interest such as hepatic dysfunction, ventricular arrhytmias, blurred vision, and vasculitis.
6. Associated signs and symptoms will be listed in the datasets as separate AE's, rather than under an umbrella diagnosis.
7. AE's for patients in study 3014 will be captured as diagnoses unless investigators reported only signs/symptoms. For the AE's of special interest, both diagnosis and associated signs and symptoms are included in the CRF page.
8. A master spreadsheet referencing specific datasets used to produce tables will be provided.

9. Subjects taking CYP3A4 and CYP2D6 substrates will be flagged by a "yes/no substrate for enzymes".
10. Subjects taking HMG Co-A reductase inhibitors will be flagged.
11. Tables will display rates of all AE's as well as AE's of special interest in subjects taking CYP3A4 inhibitors. These tables will separate subjects according to degree (weak, moderate, or strong) of enzyme inhibition.
12. For study 3014, listings will be provided for ID# , for all subjects who had:
    a. An ECG performed or any type of cardiac arrhythmia.
    b. AST, ALT, alkaline phosphatase, total bilirubin, creatinine kinase >3xULN.
    c. AST or ALT > 5x ULN.
    d. Vasculitis.
    e. Blurred vision.
13. A Pediatric Development Plan will be included in the resubmission. This plan should address all pediatric ages, and include proposed waivers/deferrals for certain ages when justified. Protocols do not need to be submitted at this time.
14. Study 3017 (Japan) has no pharmacokinetic (PK) assessments and only efficacy narratives will be provided in English.
15. All new clinical pharmacology reports will be submitted in PDF format, where the text could be copied (no scanned images where possible).
16. All individual data parameters from PK studies will be submitted (e.g., PK, concentration vs. time, ECG, etc.).
17. Hard copies (12) of the 1.1 volume of the resubmission will be provided.
18. Annotated and final copy of the labeling will be provided in Word format.
19. For the Clinical Microbiology section of the submission:
    a. An overview will be provided for all new studies.
    b. Where the information is derived from old studies, its location on the original submission will be provided.
    c. A new database integrating the new and old studies will be provided. Links to the old information and references will be included.
    d. No change in breakpoints is expected at this time.
    e. Information will be provided as requested by the Division in fax dated March 6, 2002.

ACTION ITEMS

1. A new meeting will be scheduled to describe the electronic entry system for study 4003.
2. A telecon will be scheduled to address the chemistry questions forwarded to the sponsor on March 11, 2002.
3. The sponsor will provide examples of the type of available ECG.

SPONSOR MEETING ATTENDEES

Meeting Date: March 11, 2002 2:30-4:00 p.m.

Location: Corporate, Room S300

NDA/ Name: 21-144, Ketek (telithromycin)

Sponsor: Aventis Pharmaceuticals

Type of Meeting: pre-NDA, customization of data sets

Meeting Chair: John Alexander, M.D., Medical Team Leader
Division of Anti-Infective Drug Products

Aventis Pharmaceuticals	Title
Divakar Sharma	Global Biostatistics
Michael Goedde	Project Data Manager
Steve Caffe, M.D.	Head, U.S. Regulatory Affairs
Tom Watson	U.S., Regulatory Affairs
Bruno Leroy, M.D.	Global Project Leader
Stephen Jenkins, Ph.D.	Global Head of Clinical Microbiology
Vijay Bhargava, Ph.D.	Clinical Pharmacology
Raul Villa	Global Safety Officer
Roomi Nusrat, M.D.	Global Clinical Director
Chris LeGallo	Lead SAS Programer
Division of Anti-Infective Drug Products	
Janice Soreth, M.D.	Division Director
John Alexander, M.D.	Medical Team Leader
Charles Cooper, M.D.	Medical Officer
David Ross, M.D.	Medical Team Leader
Janice Pohlman, M.D.	Medical Officer
George Rochester, Ph.D.	Statistics Reviewer
Daphne Lin, Ph.D.	Statistics Team Leader
Harold Silver	Clinical Microbiology Reviewer
Albert T. Sheldon Jr., Ph.D.	Clinical Microbiology Team Leader
Kenneth Seethaler, Ph.D.	Pharmacology Reviewer
Terry Peters, D.M.V.	Pharmacology Team Leader
Raquel Peat	Project Manager
Judit Milstein	Project Manager

BACKGROUND:

NDA 21-144 was submitted February 28, 2000, with the following indications:

5. Community-Acquired Pneumonia (CAP),
6. Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB),

7. Acute Bacteria Sinusitis (ABS), and
8. Pharyngitis/Tonsillitis (PT).

A non-approvable action was taken on June 1, 2001, for the PT indication.

An approvable action was taken on June 1, 2001, for CAP, ABECB, and ABS indications. Deficiencies included potential risks posed by the concentration-related effect of telithromycin on cardiac repolarization, hepatotoxicity, and drug exposure in patients with renal/hepatic impairment.

In order to expedite the review of the resubmission (6-months review clock), the Division and Aventis agreed to hold discussions on the format and content for the planned submission, as well as the customization of data sets.

These minutes reflect the highlights of the discussions held regarding the customization of data sets. Discussions during the meeting were based on the Division's fax dated March 6, 2002, and on the material contained in Aventis' presentations entitled "Publishing slides", "Statistics slides" and "Data Management slides."

DISCUSSION:

SUMMARY OF UNDERSTANDINGS

1. The electronic submission will be delivered according to FDA guidance "Providing Regulatory Submissions in Electronic Format-General Considerations."
2. An alphabetized master dictionary containing a description of all the variables will be provided.
3. Explanation of derived variables (direct and by reference) will be provided.
4. Every data set will have one description, containing the name, label, and location of the dataset.
5. Data sets will be constructed in a way to provide 1 row/patient, when possible.
6. Certain items (Pat. Id, TRNO, AGE, SEX, RACE) will be provided in each dataset.
7. Technical items and blank items will be removed, if not used by any program.
8. Improved logical order of variables in every dataset will be provided.
9. Aventis will provide in advance of the submission the projected size of the datasets.
10. Adverse events (AE's) will be represented with MedDRA dictionary terminology.
11. A listing will be provided of those patients in Study 3004, who were evaluated by the Clinical Events Committee (CEC), but not considered to have had an AE of special interest.
12. Smaller datasets containing laboratory data are preferable. They should have 1 row per patient with a limited number of laboratory tests (e.g., hepatic chemistries) in a single data set.
13. Text files will be provided for datasets that include narratives.

ACTION ITEMS

Aventis is willing to provide any special analysis that the Division considers necessary for the expedient review of the submission. The Division will provide Aventis with this information in a timely manner.

Judit Milstein, Regulatory Project Manager, March18, 2002

John Alexander, M.D. Medical Team Leader concurrence, May 15, 2002

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

/s/

John Alexander
7/25/02 10:51:55 AM

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 February 28, 2003. The purpose of the meeting was to discuss Aventis' proposal to address the deficiencies listed in the approvable letter dated January 24, 2003.

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 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 meeting

MEETING MINUTES

MEETING DATE: February 28, 2003

TIME: 11:30 a.m.-1:00 p.m.

LOCATION: Corporate Building, Conference Room S-300

APPLICATION: NDA 21-144/Ketek (telithromycin)

TYPE OF MEETING: Guidance

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION
Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV (ODE IV)
Edward Cox, MD, Deputy Director, ODE IV
Janice Soreth, MD, Director, Division of Anti-Infective Drug Products
John Alexander, MD, MPH, Medical Team Leader
David Ross, MD, PhD, Medical Team Leader
Janice Pohlman, MD, Medical Officer
Thomas Smith, MD, Medical Officer
Alma Davidson, MD, Medical Officer
Charles Cooper, MD, Medical Officer (via telephone)
George Rochester, PhD, Statistician
Daphne Lin, PhD, Statistics Team Leader
Jenny Zheng, PhD Biopharmaceutics Reviewer
Philip Colangelo, PhD, Biopharmaceutics Team Leader
Harold Silver, Microbiologist
Albert Sheldon, PhD, Microbiolgy Team Leader
Terry Peters, DVM, Pharm/Tox Team Leader
Andy Yu, Chemistry Reviewer
David Roeder, Associate Director for Regulatory Affairs, OND III
Judit Milstein, Regulatory Project Manager
Brenda Friend, RPh, JD, Consumer Safety Officer, DSI
Ni Khin, MD, Medical Officer, DSI
Wiley Chambers, MD, Deputy Director, DAIAODP
Mohamed Huque, PhD, Director, Division of Biometrics III

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
Larry Bell, MD – Head, Worldwide Regulatory Affairs
Steve Caffe, MD – Head, US Regulatory Affairs
Sharmila Chaudhuri – Data Management
Helen Edelberg, MD, MPH - US Regulatory Liaison
Nadine Grethe – Global Clinical Operations
Parvis Hamedani, MD – Head, Global Clinical Development, Anti-Infective Drugs
Paul Lagarenne, MD – Head, Worldwide Pharmacovigilance
Bruno Leroy, MD – Global Project Leader
Roomi Nusrat, MD – Global Clinical Development
John Pakulski, RPh – US Regulatory Coordination
Mark Quigley, PhD – Head, Worldwide Quality Assurance

Sol Rajfer, MD – Head Worldwide Clinical Development
Kristen Sharma, MD – Pharmacovigilance
Divakar Sharma, PhD – Head, Biostatistics, Anti-Infectives
Michael Shoemaker, PhD – Head, Global Clinical QA
William Stager, PhD – Biostatistics

BACKGROUND

An approvable action was taken on Ketek on January 24, 2003. Terms of this letter included a request for additional data and analyses in the areas of safety, clinical pharmacology, and labeling.
Aventis requested a meeting to clarify the questions raised in the approvable letter (**bolded text** below) and to reach agreement on the approach to addressing these questions. A briefing package containing Aventis' proposal to address the deficiencies was submitted on February 18, 2003.
Aventis also requested comments on the proposed protocol designed to evaluate the implementation of the Monitoring Plan and Auditing Plan used for Study #3014 and to assess the impact of observed deviations on the validity of the Study #3014 safety data relating to adverse events of special interest (AESIs). The Division informed Aventis prior to the meeting that comments on this protocol would not be addressed at the February 28, 2003, considering the short time elapsed between submission of the protocol and timing of the meeting.

These minutes reflect the highlights of the discussion held at this meeting. Unless otherwise specified, the Division concurs with Aventis' proposed response to the deficiencies indicated in the action letter.

Q1A1

Study #3014 – "A Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin [Ketek] and Amoxicillin-Clavulanic Acid [Augmentin] in Outpatients with Respiratory Tract Infections in a Usual Care Setting".

1) In order to assess overall data integrity and to determine what role Study #3014 can have in support of your marketing application, you must provide the following information:

(a) A list of the sites at which Aventis and/or any contract research organization (CRO) conducted quality assurance audits or monitoring visits, the dates of these audits/visits, and copies of the findings. These should be sorted by site and arranged chronologically within each site. To assist in finding individual sites, the document should be indexed.

(b) Records of any communications between Aventis and any CRO regarding any irregularities.

(c) Information on any specific steps taken post-monitoring to address irregularities.

Aventis indicated that auditing of he conduct of study # 3014 did not show significant deviations from Good Clinical Practices (GCP), and that review of the issues addressed in the 483 forms for Dr. [redacted] did not raise any concerns about the conduct of the study.

The Office of Drug Evaluation IV (ODEIV), and the Division consider the review of Aventis' monitoring plan in conjunction with [redacted] as supporting information and that review of all the data as requested in the action letter is necessary to evaluate the data integrity of study #3014. Review of this data will determine if additional sites will be inspected by the Division of Scientific Investigations (DSI).

The Division is aware of the volume of documents involved, and requested that the information on Drs —— , sites be submitted first. It was also suggested that —— could review the monitoring derived from these sites, to be able to further understand the requirements and scope of their monitoring review. Review of this data will determine if information for additional sites will be requested.

The Division also indicated that proper conduct of a study must include among other components, enrollment of patients with the disease under study, administration of study medication as described in the protocol, follow-up and collection of protocol-specific clinical and laboratory data.

The Division indicated that the protocol proposed for the —— monitoring plan lacks a definition of success and that an algorithm for what constitutes a significant deviation from the protocol needs to be explicitly defined. The Division will work with Aventis to refine the protocol.

Factors that the Division evaluates when deciding an inspection sites may include:

- Enrollment of patients without infections
- Patients returning for follow-up visits
- Missing laboratory data
- Enrollment of family or staff members
- Patients being followed up after report of adverse events (AEs)
- Sites with large number of patients relative to the total population of the area of enrollment
- Large sites with low number of AEs

If the integrity of the data for study #3014 cannot be assured, this study may not support the safety of telithromycin. In that case, the Division will have to rely on the data from post-marketing surveillance for the determination of the safety of the product and proposed labeling.

Q1A2

Submit analyses for Study #3014 pooling the following MedDRA preferred terms: Vision blurred, accommodation disorder, visual disturbance not otherwise specified (NOS), visual acuity reduced, vision abnormal NOS, visual hallucinations, diplopia, binocular eye movement disorder. In these pooled analyses, provide the following information: overall incidence rate regardless of attribution, rate of discontinuation, rate of serious adverse events, rate for men vs. women, and the relative frequency of mild, moderate and severe events. Present these analyses for both telithromycin and comparator.

Q1A3

Provide analyses for Study #3014 addressing the issue of onset and duration of visual AEs (including the following MedDRA preferred terms: Vision blurred, accommodation disorder, visual disturbance NOS, visual acuity reduced, vision abnormal NOS, visual hallucinations, diplopia, binocular eye movement disorder). With regard to duration of the AE, these analyses should be presented for two separate groups: those patients who continued the medication and those who discontinued. These analyses should describe the duration of symptoms in those patients who discontinued the drug as well as in those who continued the drug. Provide descriptive statistics (e.g., mean, median, range) of the time of onset of visual abnormalities after the start of treatment. Present these analyses in terms of hours, if possible, otherwise present them

in terms of days. Also, provide the number of visual AEs that began on each day of therapy. Provide an analysis of the duration of the pooled visual AEs by day of onset.

The following Division comments pertain to both Q1A2 and Q1A3

Include in the analysis ALL adverse events effecting vision. The complete list is as follows:

Vision Blurred
Visual Acuity Reduced
Diplopia
Hallucination, visual
Visual disturbance NOS
Vision Abnormal NOS
Asthenopia
Hallucination NOS
Accommodation disorder
Binocular eye movement disorder NOS
Chromatopsia

The following additional analyses of the visual events would be helpful in labeling this product.

Assess the duration of visual adverse events after the last dose of telithromycin. This analysis should include separately patients who discontinued telithromycin and those patients whose visual adverse events continued until completion of therapy.

Assess the rate of resolution on therapy of visual adverse events for those patients who continued telithromycin despite the visual adverse events.

Assess the time to resolution and severity of visual adverse events according to number of doses received.

Q1B1
Post-Marketing Data

1) **Data provided as narratives are incomplete. In order to better assess the post-marketing data, provide an accurate and complete English translation for original and follow-up Adverse Event (AE) reports for all post-marketing reports received as of January 31, 2003, in all countries where telithromycin has been approved. This submission should contain all original and follow-up post-marketing reports, without regard to causality. These reports should be indexed by manufacturer report number and provided as a separate bookmarked pdf file. This information should also be provided in the form of SAS transport files. These files should include line listings with all variables contained in the post-marketing SAS transport file dated December 13, 2002. Additionally, include any variables contained in the MedWatch form (Form 3500) not already contained in the SAS transport files. Provide a data dictionary defining all variables and possible variable responses.**

Provide narratives of all adverse events, not just the "serious, associated adverse events". Include a variable to relate these AEs to a specific country of origin.

Q1B3
Provide updated information on telithromycin exposure by country (including the source of these data) through January 31, 2003.

Aventis confirmed that the format and calculation method would be the same as the ones used in the Periodic Safety Update Report (PSUR).

Q1B4
In addition, while you are preparing a complete response to this letter and while the submission is under review, provide on a monthly basis all AE reports (as described above) and updated information on telithromycin exposure by country received after January 31, 2003.

Include in this report all new AEs, including clinical and follow-up cases. The report should also include the growing cumulative AEs by System Organ Class (SOC).

Q1B5
Provide a description of the amount of repeated use of telithromycin that has occurred in post-marketing use. Describe how the amount of repeated use was determined. Include any safety information available on patients who received repeated courses of telithromycin.

During the examination of AE profiles of specific events, include visual AEs, in addition to the proposed hepatic events, allergic reactions/hypersensitivity, and vasculitic events.

Q1B6
Submit the protocol for the intensified monitoring survey instituted in Germany (Study #5001; "An Open Observational Survey in Outpatients with Pharyngitis (> 12 years of age) or Mild to Moderate CAP, AECB or ABS (> 18 years of age)"). Provide in this submission a report of the findings.

Provide narratives of all adverse events, not just the "serious, associated adverse events".

Q1B2, Q1B7, Q1C1, Q1C2, Q2A, Q2B, Q3A1, A2, A3, Q3B-G

The Division concurs with Aventis proposal for these questions.

Judit Milstein, Regulatory Project Manager, March 21, 2003

David Ross, MD, PhD, Medical Team Leader concurrence, March 21, 2003

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/s/

Judit Milstein
4/7/03 08:49:19 AM

David Ross
4/14/03 01:40:21 PM
2/28/03 Minutes of the meeting