Appendix A

QT Prolonging Drugs / Drug Classes

Class	Drug
Antiarrhythmic Drugs	Amiodarone, Bretylium, Dofetilide, Disopyramide, Ibutilide, Procainamide, Quinidine, Sotalol
Psychiatric Drugs	Amitriptyline, Chlorpromazine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lithium, Maprotiline, Nortriptyline, Pimozide, Prochlorperazine, Sertindole, Thioridazine, Trifluoperazine
Antimicrobial Drugs	Amantadine, Clarithromycin, Chloroquine, Cotrimoxazole, Erythromycin, Gatifloxacin, Grepafloxacin, Halofantrine, Ketoconazole, Levofloxacin, Pentamidine, Quinine, Sparfloxacin
Antihistamines	Astemizole, Diphenhydramine, Hydroxyzine, Terfenadine
Miscellaneous	Cisapride

QT Prolonging drugs were considered individually when possible. Data entry was considered by pharmacological class for some drugs, tricyclic antidepressants for example.

Contraindicated Drug Interactions

Drug	Labeled Contraindication / Drug Interaction
Azithromycin	
Clarithromycin	Cisapride, Pimozide, Terfenadine
Dirithromycin	Terfenadine
Erythromycin	Astemizole, Cisapride, Terfenadine

Appendix B: Subjective Variables

1. "Quality of Report" Criteria

Quality – subjective evaluation based upon quantity and quality of information available, based upon the contents expected of a reasonable and prudent report.

1 = ***excellent*** (all drug, dates, QT, and relevant information available and understandable)
2 = ***above "normal"***
3 = ***normal*** (the expected "norm," – perhaps QT missing, but clear documentation of event)
4 = ***suboptimal***
5 = ***poor*** (gross under-representation of data, perhaps simply "torsade de pointes" stated)

2. "Degree of Causation"

Causal – subjective evaluation based upon how likely you believe there is a causal relationship

1 = ***strongly suspect*** (high degree of certainty [temporal, QT, no strong DI])
2 = ***likely*** (EKG documentation, potentially due to DI, some other confounder)
3 = ***possible*** (suspect drug with multiple comorbidities/confounders)
4 = ***questionable*** (questionable data, other pharmacodynamic interactions)
5 = ***doubtful*** (likely due to another etiology, strongly suspect causality)

CC: M. Goldberger
R. Albrecht
J. Cintron
D. Ross
L. Gavrilovich
S. Kweder

APPEARS THIS WAY
ON ORIGINAL

/s/

Douglas Shaffer
2/27/01 08:23:35 AM
MEDICAL OFFICER

Kathleen Uhl
2/27/01 01:34:19 PM
MEDICAL OFFICER

NDA 21-144

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:** 00-0101
March 24, 2000	August 30, 2000	

TO: Gary Chikami, M.D.
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Jose R. Cintron, Project Manager
HFD-520

PRODUCT NAME:	**MANUFACTURER:** Aventis Pharmaceuticals, Inc.
Ketek (Telithromycin Tablets) 400 mg **NDA#: 21-144**	

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), OPDRA conducted a review of the proposed proprietary name "Ketek" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the proprietary name, Ketek. See the checked box below. We have also made recommendations for labeling revisions.

☒ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **August 24, 2000**

NDA NUMBER: **21-144**

NAME OF DRUG: **Ketek (Telithromycin Tablets) 400 mg**

NDA HOLDER: **Aventis Pharmaceuticals, Inc.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Infective Drug Products (HFD-520) for assessment of the tradename Ketek, regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION
Ketek contains the active ingredient telithromycin, a synthetic ketolide antibacterial. Ketek is indicated for the treatment of infections caused by susceptible strains of the following designated common pathogens, including resistant strains of *S. pneumoniae*, and atypical pathogens in the specific conditions listed below for patients 18 years old and above, except in tonsillitis/pharyngitis in which Ketek is indicated for patients 13 years old and above:

Community acquired pneumonia due to *S. pneumoniae*, including strains resistant to penicillin and erythromycin, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, and/or *M. pneumoniae*.

Acute bacterial exacerbation of chronic bronchitis due to *S. pneumoniae, H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus,*

Acute sinusitis due to *S. pneumoniae*, including strains resistant to penicillin and erythromycin, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, and/or *S. aureus*.

Tonsillitis/Pharyngitis due to *S. pyogenes* in patients 13 years old and above.

Ketek tablets can be administered with or without food. No dosage adjustments are required for patients with impaired renal function or hepatic function. Ketek will be supplied as a 400 mg tablet in bottles of 100 and 10 tablet blister cards containing 5 days of therapy. The usual daily dose is *800 mg once daily* for all indications, however the *duration of therapy differs depending on the indication.* Community acquired pneumonia requires 7 to 10 days of therapy while the other indications require only 5 days.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Ketek to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Ketek. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Two product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Ketek. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns about the name with regard to promotional claims.

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

TABLE 1

Product Name	Dosage form(s), Generic Name	Usual adult dose*	Other**
Ketek	**Telithromycin Tablets, 400 mg**	**800 mg once daily for 5 days for all indications except for Community acquired pneumonia. This requires 800 mg once daily for 7 to 10 days.**	
Keflex	Cephalexin for Oral Suspension – 125 mg/5 mL and 250 mg/5 mL Cephalexin Capsules – 250 mg and 500 mg	250 mg q6h or 500 mg q12h.	S/A, L/A per OPDRA
K-Tab	Potassium Chloride Extended-release Tablets, 750 mg of potassium chloride equivalent to 10 mEq.	50 to 100 mEq per day.	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

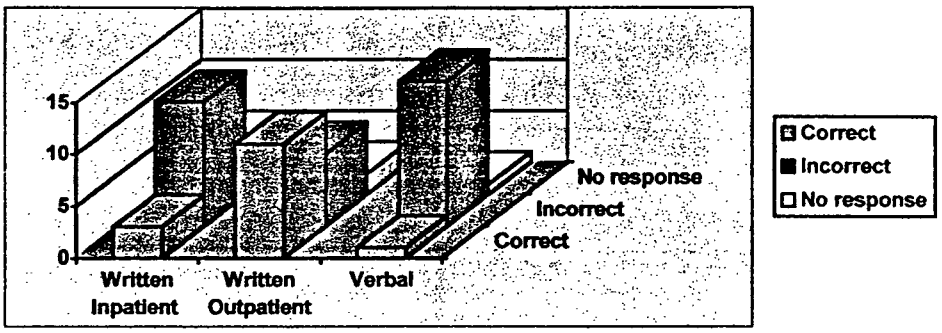
Three separate studies were conducted within FDA, to determine the degree of confusion of Ketek with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 92 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Ketek (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Ketek Sig: i po qd x 10 days Disp #10 No refills	Ketek, one daily for ten days, dispense 10 with no refills.
Inpatient: Discharge home today. Meds: Ketek 1 tab po q.d. x 10 days #10	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Ketek" Response	Other Response	No Response
Written: Outpatient	31	20 (65 %)	11 (55%)	7 (35 %)	2 (10 %)
Inpatient	31	15 (48 %)	3 (20 %)	12 (80 %)	0 (0 %)
Verbal: Outpatient	30	16 (53 %)	1 (6 %)	14 (88 %)	1 (6 %)
Total:	92	51 (55 %)	15 (29 %)	23 (45 %)	3 (6 %)



Among participants in the two written prescription studies, fourteen out of 35 study participants (40 %) interpreted the name correctly. The majority of the respondents provided misspelled variations of the drug name. According to the *outpatient written study* results, eleven study participants interpreted the name as *Ketek*. Other interpretations include: *Vetek, Kitek, and Vitek.* In the *inpatient written study*, only three participants interpreted the name correctly. Eleven participants responded with the interpretation *"Keter"*, misinterpreting the last letter "k" as an "r" and one participant responded with *"Ketel"*, misinterpreting the last letter as an "l".

Among verbal prescription study participants, only one out of fourteen participants (6 %) interpreted the name correctly. Most of the name interpretations were phonetic variations of the proprietary name; 4 study participants interpreted the name as *Cutec*; other interpretations include *Ketec, Qtek, Cuteck, Quetec and Kewtek.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Ketek", the primary concerns raised were related to a couple of sound-alike, look-alike names that already exist in the U.S. marketplace. Two products, Keflex and K-tab were believed to be the most problematic in terms of potential medication error.

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was no confirmation that Ketek could be confused with Keflex or K-tab.* The results of the verbal and written analysis studies demonstrate fifteen out of fifty-one participants (29%) interpreted the proprietary name Ketek correctly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name.

Keflex and Ketek are both antibiotics that look similar when scripted and will also be prescribed in a similar practice setting. Despite these similarities, OPDRA believes the potential for confusion is low because they *do not* share an overlapping strength, dosage form, or dosing interval. K-tab and Ketek share overlapping dosage forms and could sometimes share overlapping dosing intervals of once daily, however they do not share overlapping strengths. K-tab is also dosed on a "mEq" basis rather than "mg".

The majority of the incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name and did not overlap with a currently marketed drug product. Lastly, the proprietary name does not contain a USAN stem.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. GENERAL COMMENT

We note that the dosage form is not included in the established name. We recommend the inclusion of "Tablets" in the established name.

B. CONTAINER (100s and 10 tablet blister card)

1. The strength on the blister card <u>main</u> panel should be relocated so it appears in closer proximity to the product name.

2. *Delete the* [redacted] from the side panel of the bottle of 100s and the back panel of the blister card, as this material is promotional in tone.

3. We note the blister packaging configuration contains only ten tablets, a quantity sufficient for a five day course of therapy. *Three* of the *four* indications can be successfully treated within this time frame, the other requiring seven to ten days of medication. Recent post-marketing experience with another antibiotic, Avelox, in which the sponsor had a similar packaging configuration, a patient administered the entire contents of the container in one day rather than five days. We therefore recommend the [redacted] be highlighted on the product labeling. The "Directions For Use" on the inside panel should be revised as follows:

   Take two tablets (at the same time) once a day [redacted]

4. Revise the "DOSAGE AND ADMINISTRATION: Read package..." statement to read as follows:

   Usual Dosage: Take two tablets once daily —

5. We prefer that the — appear prominently on the main panel.

C. INSERT

See comment 2 under CONTAINER.

IV. RECOMMENDATIONS

A. OPDRA does not object to the use of the proprietary name "Ketek".

B. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph, Project Manager at 301-827-3161.

/S/

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-144
HFD-520; Division Files/Jose Cintron, Project Manager
HFD-520; Gary Chikami, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management
HFD-400; Peter Honig, Director, OPDRA
HFD-040; Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-440; Mary Dempsey, Project Manager, OPDRA
HFD-400; Sammie Beam, Project Manager, OPDRA

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5 Draft Labeling Page(s) Withheld

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MEGA/CDER

JFM 4/1/04

Milstein, Judit

m: Helen.Edelberg@aventis.com
it: Thursday, April 01, 2004 10:09 AM
To: milsteinj@cder.fda.gov
Subject: NDA 21-144 KETEK (Telithromycin): Phase IV Postmarketing Commitments (Revised April 1, 2004)

N-000 (US)
ORIG AMENDMENT

Importance: High

Dear Judit,

Reference is made to the March 30, 2004, teleconference between the DAIDP (Dr. Janice Soreth, Dr. John Alexander, Ms. Judit Milstein) and Aventis (Dr. Larry Bell, Dr. Steve Caffé, Dr. Helen Edelberg, Dr. Lourdes Frau, Dr. Paul Lagarenne, and Dr. Wanju Dai) and subsequent e-mail correspondence between Ms. Judit Milstein and Dr. Helen Edelberg regarding Phase IV postmarketing commitments for Ketek (telithromycin). Aventis commits to submitting the following items to the Agency as Phase IV postmarketing commitments for Ketek (telithromycin): Commitment # 1: Information to support the ·diatric use of telithromycin for the treatment of Acute Bacterial Sinusitis in pediatric patients less an 18 years of age.
Final Report Submission: March 31, 2008
Commitment # 2: Information to support the pediatric use of telithromycin for the treatment of Community-Acquired Pneumonia in pediatric patients less than 18 years of age.
Final Report Submission: March 31, 2008
Commitment # 3: Submit an updated assessment of all post-marketing visual adverse events that are reported globally for the first eighteen months after U.S. launch. This assessment will include detailed information regarding the nature of the visual adverse event, duration, resulting sequelae, if any, and description of any formal diagnostic evaluations to assess this event. Particular attention will be paid to patients whose symptoms did not resolve promptly. Information on the patients in question including but not limited to underlying diseases and concomitant medications should also be submitted. Final Report Submission: March 31, 2006

Please feel free to contact me with any questions or concerns. Thank you Helen

Helen K Edelberg, MD, MPH
GDDC/US Regulatory Liaison
Tel: (908) 304-6345
Fax: (908) 304-6318
Mobile: (908) 601-4843

ORIGINAL

NDA 21-144
4S

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MEGA/CDER

3/31/04

Milstein, Judit

m: Helen.Edelberg@aventis.com
t: Wednesday, March 31, 2004 9:33 AM
To: milsteinj@cder.fda.gov
Subject: NDA 21-144 KETEK (Telithromycin): Phase IV Postmarketing Commitments

Importance: High

Dear Judit,

Reference is made to the March 30, 2004, teleconference between the DAIDP (Dr. Janice Soreth, Dr. John Alexander, Ms. Judit Milstein) and Aventis (Dr. Larry Bell, Dr. Steve Caffé, Dr. Helen Edelberg, Dr. Lourdes Frau, Dr. Paul Lagarenne, and Dr. Wanju Dai) and subsequent e-mail correspondence between Ms. Judit Milstein and Dr. Helen Edelberg regarding Phase IV postmarketing commitments for Ketek (telithromycin). Aventis commits to submitting the following items to the Agency as Phase IV postmarketing commitments for Ketek (telithromycin): Commitment # 1: Information to support the pediatric use of telithromycin for the treatment of Acute Bacterial Sinusitis in pediatric patients less than 18 years of age.
Final Report Submission: March 31, 2008
Commitment # 2: Information to support the pediatric use of telithromycin for the treatment of Community-Acquired Pneumonia in pediatric patients less than 18 years of age.
Final Report Submission: March 31, 2008
Commitment # 3: Submit an updated assessment of all post-marketing visual adverse events that occurred in USA and abroad over the first eighteen months of U.S. approval. This assessment will include detailed information regarding the nature of the visual adverse event, duration, resulting sequelae and description of any formal ophthalmic evaluations. Particular attention will be paid to patients whose symptoms did not resolve promptly.
Final Report Submission: March 31, 2006
Please feel free to contact me with any questions or concerns. Thank you, Helen Helen K Edelberg, MD, MPH GDDC/US Regulatory Liaison
Tel: (908) 304-6345
Fax: (908) 304-6318
Mobile: (908) 601-4843

MEMORANDUM OF TELECON

DATE: March 15, 2001

APPLICATION NUMBER: NDA 21-144, Ketek (telithromycin)

BETWEEN:

Name: Dr. Mindell Seidlin
Dr. Bruno Leroy
Dr. Kristen Sharma
Dr. William Stager
Dr. Charlie Chen
Dr. Abdel Oualim
Dr. Jean-Christophe LeMarie
Dr. Nadine Godfroid
Ms. Mary Elicone

Phone: (888) 795-9168
Representing: Aventis

AND

Name: Ms. Beth Duvall-Miller, Regulatory Health Project Manager
Dr. Ed Cox, Medical Officer
Dr. David Ross, Medical Officer
Dr. George Rochester, Statistical Reviewer
Dr. Joyce Korvick, Acting Medical Team Leader
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Clarification of information submitted in February 28, 2001 major amendment

Background:

Aventis is the sponsor of NDA 21-144 for Ketek (telithromycin), submitted February 28, 2000. — is the contract research organization responsible for this application. On Feburary 28, 2001 — submitted a major clinical amendment which extended the user fee goal date to June 1, 2001. On March 14, 2001, FDA phoned Aventis' — to ask for clarification of datasets submitted in the amendment as well as to request additional information for the purposes of FDA review. This telecon was held to allow Aventis' — to respond to the items requested on March 14. Prior to the telecon, Aventis faxed their response for the purposes of discussion in this teleconference **(attached)**.

Discussion:

Liver tables requested by Dr. Cox (#6 in Aventis facsimile): Aventis explained that the liver tables to which Dr. Cox referred were inadvertently omitted from the February 28, 2001

amendment. Dr. Cox asked if Aventis could also provide tables similar to those submitted in the original NDA (e.g., men vs. women, stratified by age, and stratified by weight > and < 50 kg) for patients in the community-acquired pneumonia (CAP) studies. Aventis agreed to determine if those tables are included in the submission or else they will provide the requested tables for Dr. Cox. Dr. Cox also requested that Aventis submit tables with respect to liver abnormalities (in the Phase 1 studies) and offered to fax this request later to [redacted]

Disparity in number of safety evaluable subjects (#1 in Aventis facsimile): Aventis explained that the disparity between safety evaluable patients in the REFER dataset and the ISS submitted February 28, 2001, is due to study centers that were censored per FDA investigations. FDA acknowledged this explanation and requested that Aventis [redacted] submit a REFER database (SAS transport file) with a variable to flag censored patients.

Transition from enrolled status to safety evaluable status (#2 in Aventis facsimile): Dr. Ross asked for clarification of why patients who were enrolled were not considered part of the safety evaluable population in the ISS. Aventis explained that there was no baseline safety assessment in those patients. Dr. Ross requested that Aventis provide him with more details about the "missing" data (56 patients who were treated but not safety evaluable + 24 patients who were randomized but not treated = 80 patients total) and that they provide FDA with a SAS transport file for these patients that includes the patient identification numbers as well as variables to flag censored patients and randomized versus treated patients. Aventis agreed to provide FDA with these files both with and without censored patients.

Full datasets in February 28, 2001 submission (#3 in Aventis facsimile): Dr. Ross requested that Aventis/ [redacted] submit a new REFER database (SAS transport file) and a "lab_megadataset" database with a SUBJSTAT variable and a variable to flag for censored patients. Dr. Ross asked that this latter dataset be broken down by type of lab across all studies. FDA said that they would follow up this request with a facsimile that clarifies this request.

ECG request (#4 in Aventis facsimile): Previously, FDA requested that Aventis/ [redacted] submit the ECG for patient# 0009, site 537, study 3010. Aventis/ [redacted] noted that the requested ECG was sent by FedEx on March 14, 2001 to Mr. Jose Cintron's attention. Dr. Ross requested ECGs for two additional patients who died in clinical studies: patient # 1520 (65 year old M), site 803, study 3000 and patient # 0004 (80 year old M), site 1301, study 3001. Aventis agreed to this request.

All subjects in study 3010 assigned to "Not treated" treatment group in REFER ISS/ISE database (#5 in Aventis facsimile): Aventis confirmed for Dr. Ross in their facsimile that this issue was due to a SAS programming decoding error that impacts the SAS export files but not the SAS tables or ISS conclusions. FDA understood this response and the corrective measure to be taken (replace the value for "other – not treated" with "11 – HMR 3647 7 days" in the D_TRNO programming code). Aventis acknowledged that this affected 430 patients in the REFER ISS/ISE database submitted February 28, 2001. FDA noted that they would have to verify the safety database after this correction.

Action Items:

1. Aventis — to submit updated REFER database (SAS Transport file) with variables described above.

2. Aventis — to submit SAS Transport file of 80 patients who were not included in the safety evaluable dataset, with variables described above, and to provide more details as to why they were not included in the safety evaluable dataset.

3. Aventis — to submit "lab_megadataset" (SAS Transport file), to be broken down by type of lab across all studies, with variables described above. FDA to follow-up with facsimile that specifies this request.

4. Aventis — to submit ECGs for two additional Ketek-treated patients who died, along with chart notes if available. Aventis — to also provide chart notes on patient (#0009) whose ECG was previously requested.

5. Aventis — to provide FDA with liver tables requested by Dr. Cox. FDA to follow-up with facsimile that specifies this request.

FDA reminded Aventis — that all information, including the facsimile sent in advance of this telecon (attached), should be submitted formally to NDA 21-144. Aventis — agreed to this request.

/S/

Beth Duvall-Miller
Regulatory Health Project Manager

Attachment: Aventis facsimile dated March 15, 2001 (25 pages)

To: Beth Duvall-Miller From: —

Company: [redacted] Date: 3-15-01

Fax No: [redacted] 301-827-2325 Page 1 of: 25

SUBJECT:

NDA 21-144

—

Materials for Teleconference

/S/

Response to Dr. Ross's questions

1. **The REFER data set submitted contains 6 113 subjects. When selecting safety evaluable subjects by using the variable SUBJSTAT, the number obtained (5 113) does not match the number reported in the Integrated Safety Summary (4 937).**

The REFER data set submitted contains data of all subjects enrolled in the 13 Phase III clinical trials. Among these 6 113 subjects, a total of 5 113 were flagged as safety evaluable in the REFER data set according to the ISS definition [section 8.5.2.2, 1:v114:p007: subjects who received at least one dose of study treatment and had least one safety assessment following randomization (or assignment for open studies)].

FDA identified investigators to be censored from efficacy/safety evaluation. The list of the 8 centers is the following:

Study	Centers
3005	150, 191
3007	63, 104
3009	281, 301
3011	607*, 726**

* same investigator as 63 in study 3007
** same investigator as 191 in study 3005

The Integrated Safety Summary reports only data of safety evaluable subjects of non-censored centers. This leads to a total of 4 937 subjects.

Table v06/0000034x.lst (attached to this document) display counts of subjects enrolled, randomized/assigned, treated and safety evaluable by indication, study, treatment group for the 6 113 subjects enrolled in the 13 Phase III studies. Table v06/0000035x.lst displays the same counts for the 5 909 enrolled subjects remaining after censoring the 204 subjects enrolled in the 8 centers excluded by FDA.

In summary, the counts of the different populations are the following:

Population	No censoring	Excluding censored centers
Enrolled	6 113	5 909
Randomized/assigned	5 193	4 998
Treated	5 169	4 985
Safety evaluable	5 113	4 937

Individual data (from REFER data set) of the 204 subjects enrolled in centers excluded by FDA are displayed in patient listing v06/00000022t.lst (attached to this document). In these 204 subjects 176 are flagged as safety evaluable in the REFER data set. Distribution per study of the 204 and 176 subjects is the following:

Censored	CAP/3009	AECB/3007	SIN/3005	SIN/3011	Total
In enrolled	25	124	38	17	204
In safety evaluable	25	116	35	0	176

It must be noted that from the 17 subjects enrolled in centers 607 and 726 of 3011, 6 were not randomized and 11 were randomized. These 11 subjects randomized were actually treated but were flagged as 'not treated' in the REFER data set (see study report, section 5.1, 1:v073:p112-113). Therefore none of the 11 subjects is counted in the 5 169 treated subjects. Since none of these 11 subjects is counted as treated, none of them is counted as safety evaluable.

In conclusion, all ISS tables submitted in the Major Amendment were correctly prepared from the population of the 4 957 subjects evaluable (censoring centers identified by FDA).

2. **Details about transition from enrolled status to safety evaluable status**

From the first summary table above, differential counts can be derived:

Population	No censoring	Excluding censored centers
Randomized/assigned But not treated	24	13
Treated but not safety evaluable	56	48

Once again a special mention must be made for the 11 subjects randomized/treated in sites 607 and 726 of 3011. Due to their flagging as 'non treated' they are counted in the 24 'randomized/assigned but not treated' in the table above, they are not counted in the 56 'treated but not safety evaluable'.

Patient listings v06/00000023t.lst and v06/00000024t.lst (attached to this document) provide individual data (from REFER data set with addition of flagging for centers excluded by FDA) for the 24 subjects randomized/assigned but not treated (including the 11 randomized/treated subjects of 3011 mentioned above) and for the 56 subjects treated but not safety evaluable, respectively. As shown by the REFER variable D_EVS1, none of the 56 subjects (treated but not safety evaluable) has a post baseline safety assessment available (i.e. no post baseline data available for adverse events, laboratory data, vital signs, ECGs or physical examination).

3. **Rationale detailing why Aventis sent full datasets to FDA (including the censored sites)**

The datasets submitted in the major amendment contained all subjects including those from censored sites to fully disclose all data and be consistent with the original NDA submission.

Following the agreement with FDA in 4Q, 2000 to censor specific investigators/sites, (centers 150 and 191 in study 3005; centers 63 and 104 in study 3007, and centers 281 and 301 in study

3009) all programs and corresponding tables used coding (instead of a flag) to exclude these subjects from the analysis.

We apologize for not adding a flag to identify the subjects from the censored investigators/sites. If requested a flag can be added to a new REFER dataset and submitted quickly.

4. **ECG request**

The ECG for patient # 0009, site 537, study 3010 was sent by Federal Express on March 14, 2001 directly from Dr. Kristen Sharma at Aventis, Bridgewater, NJ and should have arrived at the Division this morning.

5. **In response to Dr Ross finding in the ISE-ISS refer dataset that all subjects for study 3010 were assigned to "Not treated" treatment group (DTRNO is the variable name)**

Aventis confirms that this is a SAS programing decoding error that impacts the xport files but not the SAS tables or the ISS conclusions

The REFER dataset contains two variables for Treatment group: a coded variable (D_TRNO) and a decoded variable (DTRNO).

This decoded variable (DTRNO) was never used in any analysis. It was added to the xport files as specified in guidance to save time for the reviewer.
In the refer program of the 3010 study, the correct coded value "1" of D_TRNO has been wrongly decoded due to the use of the following format :

D_TRNO DECODE

1	HMR 3647 800 mg
2	Amoxicillin 1000 mg
3	HMR 3647 5 days
4	HMR 3647 10 days
5	AmoxiciLin/clavulanic
6	Penicillin V
7	Clarithromycin
8	Cefuroxim Axetil
9	Trovafloxacin
10	HMR 3647 7-10 days
other	Not treated

We apologize for the inconvenience that this has caused.

The variable used to select the treatment groups for the analysis of all ISS and ISE tables is the variable D_TRNO.
All programs used the code for D_TRNO (having possible values of 1 to 11) which is correct.

In the reporting steps of the ISS/ISE, a label of the coded value D_TRNO
is assigned in the individual programs as follows :

D_TRNO LABEL

1 HMR 3647 800 mg
2 Amoxicillin 1000 mg
3 HMR 3647 5 days
4 HMR 3647 10 days
5 Amoxicillin/clavulanic
6 Penicillin V
7 Clarithromycin
8 Cefuroxim Axetil
9 Trovafloxacin
10 HMR 3647 7-10 days
11 HMR 3647 7 days

This error occured in all datasets where study 3010 was used (Individual study datasets, All CAP studies pooled datasets and all phase III studies pooled datasets).

6. Response to Dr. Cox's questions

The liver tables which Dr. Cox referred to in the teleconference from 3/14/01 were not included in the major amendment ISS; they were programmed with the other tables and mistakenly omitted. They are attached to this document. The reference numbers are x10/0000078t, x10/0000087t (alkaline phosphatase) and x10/0000096t, x10/0000105t (total bilirubin).

The process of adding the two corresponding table values (with and without concomitant acetomenophen) was appropriate. However, as we would not like to add this inconvenience to Dr. Cox's review, we will provide the tables, as above.

Dr Cox correctly noted that some table headers in the appendix to the major amendment do not state that censored sites were excluded. Aventis can confirm that all tables contained in the major amendment excluded subjects from censored investigators/sites with the exception of tables SS163 and SS 166 to SS-173. These 7 tables show selected results from the original NDA submission and were provided for ease of reference but are not discussed in the ISS text.

Table!!*!!!!!! Subject disposition by indication including centers excluded by FDA - HMR 3647 and comparators(a)

Indication (a)/ Protocol	Enrolled	Randomized Total	Randomized HMR 3647	Randomized Comp.(b)	Treated Total	Treated HMR 3647	Treated Comp.(b)	Safety evaluable Total	Safety evaluable HMR 3647	Safety evaluable Comp.(b)
CAP										
HMR 3647A/3006	451	449	225	225	448	224	224	447	221	222
HMR 3647A/3009	312	248	124	123	248	124	124	242	121	121
HMR 3647A/3001	605	404	199	205	404	199	205	404	199	205
HMR 3647A/3000	240	240	240		240	240		239	239	
HMR 3647A/3009 OL	222	221	221		221	221		218	218	
HMR 3647A/3010	443	412	412		412	412		410	410	
Total CAP	2313	1994	1440	554	1993	1440	553	1976	1426	548
AECB										
HMR 3647A/3007	571	498	244	254	496	243	253	482	238	249
HMR 3647A/3011	335	324	163	161	321	161	160	320	160	160
Total AECB	906	822	407	415	817	404	413	802	398	404
Sinusitis										
HMR 3647A/3005	1244	791	528	261	790	528	262	778	523	255
HMR 3647A/3002	343	341	341		336	336		333	333	
HMR 3647A/3011	593	385	260	125	374	252	122	373	252	121
Total Sinusitis	2180	1517	1129	386	1500	1116	384	1484	1108	376
TONS/PHAR										
HMR 3647A/3008	526	463	232	231	461	230	231	457	229	228
HMR 3647A/3006	398	397	198	199	396	198	198	394	198	196
Total TONS/PHAR	924	860	430	430	859	430	429	851	427	424
Total for all studies	6121	5193	3406	1787	5169	3390	1779	5113	3361	1752

a CAP-community acquired pneumonia, AECB-acute exacerbation of chronic bronchitis, TONS/PHAR-tonsillitis/pharyngitis.
b Comparator study medication include: clarithromycin (HMR 3647A/3006), trovafloxacin (HMR 3647A/3009), amoxicillin (HMR 3647A/3001) in CAP studies; cefuroxime axetil (HMR 3647A/3007) and coadministration of amoxicillin and clavulanic acid (HMR 3647A/3003) in AECB studies; coadministration of amoxicillin and clavulanic acid (HMR 3647A/3005), cefuroxime axetil (HMR 3647A/3011) in sinusitis studies; clarithromycin (HMR 3647A/3008), penicillin VK (HMR 3647A/3006) in TONS/PHAR studies.

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Table!!!!!!!! Subject disposition by indication without centers excluded by FDA - HMR 3647 and comparator (a)

Indication (a)/ Protocol	Enrolled	Randomized			Treated			Safety evaluable		
		Total	HMR 3647	Comp. (b)	Total	HMR 3647	Comp. (b)	Total	HMR 3647	Comp (b)
CAP										
HMR 3647A/3006	453	449	224	225	448	224	224	443	221	222
HMR 3647A/3009	229	223	111	112	223	111	112	217	108	109
HMR 3647A/3001	405	404	199	205	404	199	205	404	199	205
HMR 3647A/3000	240	240	240		240	240		239	239	
HMR 3647A/3009 OL	221	221	221		221	221		218	210	
HMR 3647A/3010	442	412	412		412	412		430	438	
Total CAP	2009	1969	1427	542	1968	1427	541	1951	1415	536
AECB										
HMR 3647A/3007	447	376	183	191	374	182	192	364	180	186
HMR 3647A/3003	325	324	163	161	321	161	160	320	160	160
Total AECB	772	700	346	354	695	343	352	686	340	346
Sinusitis										
HMR 3647A/3005	1208	754	502	252	753	502	251	743	498	245
HMR 3647A/3002	333	341	341		336	336		333	333	
HMR 3647A/3011	516	370	252	122	374	252	122	374	252	121
Total sinusitis	2125	1469	1095	374	1467	1090	371	1449	1083	366
TONS/PHAR										
HMR 3647A/3008	526	461	232	231	461	232	231	457	229	228
HMR 3647A/3004	398	397	198	199	396	198	198	394	198	196
Total TONS/PHAR	924	850	430	430	859	430	429	851	427	424
Total for all studies	5909	4998	3298	1700	4985	3290	1695	4917	3265	1672

a CAP=community acquired pneumonia, AECB=acute exacerbation of chronic bronchitis, TONS/PHAR=tonsillitis/pharyngitis
b Comparator study medication include: clarithromycin (HMR 3647A/3006), trovafloxacin (HMR 3647A/3009), amoxicillin (HMR 3647A/3001) in CAP studies; cefuroxime axetil (HMR 3647A/3007) and coadministration of amoxicillin and clavulanic acid (HMR 3647A/3003) in AECB studies; coadministration of amoxicillin and clavulanic acid (HMR 3647A/3005), cefuroxime axetil (HMR 3647A/3011) in sinusitis studies; clarithromycin (HMR 3647A/3008), penicillin VK (HMR 3647A/3004) in TONS/PHAR studies.

HMR3647A/Ketolide Hoechst Marion Roussel v0A/00000212.lst 15 MARCH 2001 1

Listing11-13!!! Listing of subjects enrolled in centers excluded by FDA

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
CAP					
3009/0281/001	Yes	Yes	Yes	Yes	Yes
3009/0281/004	Yes	Yes	Yes	Yes	Yes
3009/0101/001	Yes	Yes	Yes	Yes	Yes
3009/0101/003	Yes	Yes	Yes	Yes	Yes
3009/0101/006	Yes	Yes	Yes	Yes	Yes
3009/0101/007	Yes	Yes	Yes	Yes	Yes
3009/0301/010	Yes	Yes	Yes	Yes	Yes
3009/0301/011	Yes	Yes	Yes	Yes	Yes
3009/0301/013	Yes	Yes	Yes	Yes	Yes
3009/0301/015	Yes	Yes	Yes	Yes	Yes
3009/0301/018	Yes	Yes	Yes	Yes	Yes
3009/0301/020	Yes	Yes	Yes	Yes	Yes
3009/0301/021	Yes	Yes	Yes	Yes	Yes
3009/0281/002	Yes	Yes	Yes	Yes	Yes
3009/0201/003	Yes	Yes	Yes	Yes	Yes
3009/0301/002	Yes	Yes	Yes	Yes	Yes
3009/0301/004	Yes	Yes	Yes	Yes	Yes
3009/0301/005	Yes	Yes	Yes	Yes	Yes
3009/0101/008	Yes	Yes	Yes	Yes	Yes
3009/0101/009	Yes	Yes	Yes	Yes	Yes
3009/0101/012	Yes	Yes	Yes	Yes	Yes
3009/0101/014	Yes	Yes	Yes	Yes	Yes
3009/0101/016	Yes	Yes	Yes	Yes	Yes
3009/0101/017	Yes	Yes	Yes	Yes	Yes
3009/0301/019	Yes	Yes	Yes	Yes	Yes

Listing [illegible] Listing of subjects enrolled in centers excluded by FDA (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
[illegible]					
3007/0063/044	Yes	No	N/A	N/A	Yes
3007/0063/051	Yes	No	No	N/A	Yes
3007/0063/002	Yes	Yes	Yes	Yes	Yes
3007/0063/003	Yes	Yes	Yes	Yes	Yes
3007/0063/006	Yes	Yes	Yes	Yes	Yes
3007/0063/008	Yes	Yes	Yes	No	Yes
3007/0063/010	Yes	Yes	Yes	Yes	Yes
3007/0063/012	Yes	Yes	Yes	Yes	Yes
3007/0063/014	Yes	Yes	Yes	Yes	Yes
3007/0063/016	Yes	Yes	Yes	Yes	Yes
3007/0063/017	Yes	Yes	Yes	Yes	Yes
3007/0063/020	Yes	Yes	Yes	Yes	Yes
3007/0063/022	Yes	Yes	Yes	Yes	Yes
3007/0063/023	Yes	Yes	Yes	Yes	Yes
3007/0063/025	Yes	Yes	Yes	Yes	Yes
3007/0063/027	Yes	Yes	Yes	Yes	Yes
3007/0063/030	Yes	Yes	Yes	Yes	Yes
3007/0063/032	Yes	Yes	Yes	Yes	Yes
3007/0063/033	Yes	Yes	Yes	Yes	Yes
3007/0063/035	Yes	Yes	Yes	Yes	Yes
3007/0063/038	Yes	Yes	Yes	Yes	Yes
3007/0063/039	Yes	Yes	Yes	Yes	Yes
3007/0063/041	Yes	Yes	Yes	No	Yes
3007/0063/045	Yes	Yes	Yes	Yes	Yes
3007/0063/047	Yes	Yes	Yes	Yes	Yes
3007/0063/048	Yes	Yes	Yes	Yes	Yes
3007/0063/052	Yes	Yes	Yes	Yes	Yes
3007/0063/054	Yes	Yes	Yes	Yes	Yes
3007/0063/056	Yes	Yes	Yes	Yes	Yes
3007/0063/058	Yes	Yes	Yes	Yes	Yes
3007/0063/060	Yes	Yes	Yes	Yes	Yes
3007/0063/061	Yes	Yes	Yes	Yes	Yes
3007/0063/063	Yes	Yes	Yes	Yes	Yes
3007/0063/065	Yes	Yes	Yes	Yes	Yes
3007/0063/067	Yes	Yes	Yes	Yes	Yes
3007/0063/068	Yes	Yes	Yes	Yes	Yes
3007/0063/071	Yes	Yes	Yes	No	Yes
3007/0063/073	Yes	Yes	Yes	Yes	Yes
3007/0063/074	Yes	Yes	Yes	Yes	Yes
3007/0063/076	Yes	Yes	Yes	Yes	Yes
3007/0063/078	Yes	Yes	Yes	Yes	Yes
3007/0063/081	Yes	Yes	Yes	Yes	Yes
3007/0063/083	Yes	Yes	Yes	Yes	Yes

Listing!!!!!!!! Listing of subjects enrolled in centers excluded by FDA* (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
AECB					
3007/0063/085	Yes	Yes	Yes	Yes	Yes
3007/0104/001	Yes	Yes	Yes	Yes	Yes
3007/0104/003	Yes	Yes	Yes	Yes	Yes
3007/0104/006	Yes	Yes	Yes	Yes	Yes
3007/0104/007	Yes	Yes	Yes	Yes	Yes
3007/0104/009	Yes	Yes	Yes	Yes	Yes
3007/0104/012	Yes	Yes	Yes	Yes	Yes
3007/0104/014	Yes	Yes	Yes	Yes	Yes
3007/0104/015	Yes	Yes	Yes	Yes	Yes
3007/0104/017	Yes	Yes	Yes	Yes	Yes
3007/0104/018	Yes	Yes	Yes	Yes	Yes
3007/0104/021	Yes	Yes	Yes	Yes	Yes
3007/0104/023	Yes	Yes	Yes	Yes	Yes
3007/0104/025	Yes	Yes	Yes	Yes	Yes
3007/0104/028	Yes	Yes	Yes	Yes	Yes
3007/0104/029	Yes	Yes	Yes	Yes	Yes
3007/0104/031	Yes	Yes	Yes	Yes	Yes
3007/0104/033	Yes	Yes	Yes	Yes	Yes
3007/0104/036	Yes	Yes	Yes	Yes	Yes
3007/0104/038	Yes	Yes	Yes	Yes	Yes
3007/0063/001	Yes	Yes	Yes	Yes	Yes
3007/0063/004	Yes	Yes	Yes	Yes	Yes
3007/0063/005	Yes	Yes	Yes	Yes	Yes
3007/0063/007	Yes	Yes	Yes	Yes	Yes
3007/0063/009	Yes	Yes	Yes	Yes	Yes
3007/0063/011	Yes	Yes	Yes	Yes	Yes
3007/0063/013	Yes	Yes	Yes	Yes	Yes
3007/0063/016	Yes	Yes	Yes	Yes	Yes
3007/0063/018	Yes	Yes	Yes	Yes	Yes
3007/0063/019	Yes	Yes	Yes	Yes	Yes
3007/0063/021	Yes	Yes	Yes	Yes	Yes
3007/0063/024	Yes	Yes	Yes	Yes	Yes
3007/0063/026	Yes	Yes	Yes	Yes	Yes
3007/0063/028	Yes	Yes	Yes	Yes	Yes
3007/0063/029	Yes	Yes	Yes	Yes	Yes
3007/0063/031	Yes	Yes	Yes	Yes	Yes
3007/0063/034	Yes	Yes	Yes	Yes	Yes
3007/0063/036	Yes	Yes	Yes	Yes	Yes
3007/0063/037	Yes	Yes	Yes	Yes	Yes
3007/0063/040	Yes	Yes	Yes	Yes	Yes
3007/0063/042	Yes	Yes	Yes	Yes	Yes
3007/0063/043	Yes	Yes	Yes	Yes	Yes
3007/0063/046	Yes	Yes	Yes	Yes	Yes

Listing!!!!!!!! Listing of subjects enrolled in centers excluded by FDA (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
ABCR					
3007/0063/049	Yes	Yes	Yes	Yes	Yes
3007/0063/050	Yes	Yes	Yes	Yes	Yes
3007/0063/051	Yes	Yes	Yes	Yes	Yes
3007/0063/055	Yes	Yes	Yes	Yes	Yes
3007/0063/057	Yes	Yes	Yes	No	Yes
3007/0063/059	Yes	Yes	Yes	Yes	Yes
3007/0063/062	Yes	Yes	Yes	Yes	Yes
3007/0063/064	Yes	Yes	Yes	Yes	Yes
3007/0063/066	Yes	Yes	Yes	No	Yes
3007/0063/069	Yes	Yes	Yes	Yes	Yes
3007/0063/070	Yes	Yes	Yes	Yes	Yes
3007/0063/073	Yes	Yes	Yes	Yes	Yes
3007/0063/075	Yes	Yes	Yes	Yes	Yes
3007/0063/077	Yes	Yes	Yes	No	Yes
3007/0063/079	Yes	Yes	Yes	Yes	Yes
3007/0063/080	Yes	Yes	Yes	Yes	Yes
3007/0063/082	Yes	Yes	Yes	Yes	Yes
3007/0063/084	Yes	Yes	Yes	Yes	Yes
3007/0063/086	Yes	Yes	Yes	Yes	Yes
3007/0104/002	Yes	Yes	Yes	Yes	Yes
3007/0104/004	Yes	Yes	Yes	Yes	Yes
3007/0104/005	Yes	Yes	Yes	Yes	Yes
3007/0104/006	Yes	Yes	Yes	Yes	Yes
3007/0104/010	Yes	Yes	Yes	Yes	Yes
3007/0104/011	Yes	Yes	Yes	Yes	Yes
3007/0104/014	Yes	Yes	Yes	Yes	Yes
3007/0104/016	Yes	Yes	Yes	Yes	Yes
3007/0104/019	Yes	Yes	Yes	Yes	Yes
3007/0104/020	Yes	Yes	Yes	Yes	Yes
3007/0104/022	Yes	Yes	Yes	Yes	Yes
3007/0104/024	Yes	Yes	Yes	Yes	Yes
3007/0104/026	Yes	Yes	Yes	Yes	Yes
3007/0104/027	Yes	Yes	Yes	Yes	Yes
3007/0104/030	Yes	Yes	Yes	Yes	Yes
3007/0104/032	Yes	Yes	Yes	Yes	Yes
3007/0104/034	Yes	Yes	Yes	Yes	Yes
3007/0104/035	Yes	Yes	Yes	Yes	Yes
3007/0104/037	Yes	Yes	Yes	Yes	Yes

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Listing!!!!!!!! Listing of subjects enrolled in centers excluded by FDA (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
Sinusitis					
3005/0150/028	Yes	No	No	No	Yes
3005/0350/001	Yes	Yes	Yes	Yes	Yes
3005/0350/003	Yes	Yes	Yes	Yes	Yes
3005/0350/004	Yes	Yes	Yes	Yes	Yes
3005/0150/006	Yes	Yes	Yes	Yes	Yes
3005/0150/008	Yes	Yes	Yes	No	Yes
3005/0150/009	Yes	Yes	Yes	Yes	Yes
3005/0150/010	Yes	Yes	Yes	Yes	Yes
3005/0150/011	Yes	Yes	Yes	Yes	Yes
3005/0150/013	Yes	Yes	Yes	Yes	Yes
3005/0150/015	Yes	Yes	Yes	Yes	Yes
3005/0150/016	Yes	Yes	Yes	Yes	Yes
3005/0150/019	Yes	Yes	Yes	Yes	Yes
3005/0150/029	Yes	Yes	Yes	Yes	Yes
3005/0150/021	Yes	Yes	Yes	Yes	Yes
3005/0150/022	Yes	Yes	Yes	Yes	Yes
3005/0150/024	Yes	Yes	Yes	Yes	Yes
3005/0150/025	Yes	Yes	Yes	Yes	Yes
3005/0150/027	Yes	Yes	Yes	Yes	Yes
3005/0150/030	Yes	Yes	Yes	Yes	Yes
3005/0150/031	Yes	Yes	Yes	Yes	Yes
3005/0350/032	Yes	Yes	Yes	Yes	Yes
3005/0350/034	Yes	Yes	Yes	Yes	Yes
3005/0150/035	Yes	Yes	Yes	Yes	Yes
3005/0150/036	Yes	Yes	Yes	Yes	Yes
3005/0191/001	Yes	Yes	Yes	Yes	Yes
3005/0191/002	Yes	Yes	Yes	Yes	Yes
3005/0150/002	Yes	Yes	Yes	Yes	Yes
3005/0150/005	Yes	Yes	Yes	Yes	Yes
3005/0150/007	Yes	Yes	Yes	Yes	Yes
3005/0150/032	Yes	Yes	Yes	Yes	Yes
3005/0150/014	Yes	Yes	Yes	Yes	Yes
3005/0150/017	Yes	Yes	Yes	Yes	Yes
3005/0150/020	Yes	Yes	Yes	No	Yes
3005/0150/023	Yes	Yes	Yes	Yes	Yes
3005/0150/026	Yes	Yes	Yes	Yes	Yes
3005/0150/029	Yes	Yes	Yes	Yes	Yes
3005/0150/033	Yes	Yes	Yes	Yes	Yes
3011/0607/002	Yes	No	No	No	Yes
3011/0607/003	Yes	No	No	No	Yes
3011/0607/004	Yes	No	No	No	Yes
3011/0607/005	Yes	No	No	No	Yes
3011/0607/006	Yes	No	No	No	Yes

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Listing[illegible] Listing of subjects enrolled in centers excluded by FDA (Confidential)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA	
Sinusitis						
3011/0607/007	Yes	No	No	No	Yes	
3011/0607/001	Yes	Yes	No	No	Yes	
3011/0607/008	Yes	Yes	No	No	Yes	
3011/0726/002	Yes	Yes	No	No	Yes	
3011/0726/007	Yes	Yes	No	No	Yes	
3011/0726/005	Yes	Yes	No	No	Yes	
3011/0726/00A	Yes	Yes	No	No	Yes	
3011/0726/007	Yes	Yes	No	No	Yes	
3011/0726/004	Yes	Yes	No	No	Yes	
3011/0607/005	Yes	Yes	No	No	Yes	
3011/0726/001	Yes	Yes	No	No	Yes	
3011/0726/004	Yes	Yes	No	No	Yes	

Listing [illegible] Listing of subjects randomized but not treated

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
CAP					
[illegible]	Yes	Yes	No	N/A	No

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Listing!!!!!!! Listing of subjects randomised but not treated (Continued)

Study r.o./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
ABCD					
1001/0705/020	Yes	Yes	No	No	No
1001/0705/042	Yes	Yes	No	No	No
1001/1706/003	Yes	Yes	No	No	No
3001/0106/002	Yes	Yes	No	N/A	No
3001/0102/003	Yes	Yes	No	N/A	No

Listing 11.1.1.1 Listing of subjects randomized but not treated (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
Sinusitis					
1002/0603/001	Yes	Yes	No	No	No
1002/0603/003	Yes	Yes	No	No	No
1002/0603/013	Yes	Yes	No	No	No
1002/0603/029	Yes	Yes	No	No	No
1002/0726/008	Yes	Yes	No	No	No
1005/0122/006	Yes	Yes	No	No	No
1011/0607/001	Yes	Yes	No	No	No
1011/0607/00A	Yes	Yes	No	No	No
1011/0726/002	Yes	Yes	No	No	Yes
1011/0726/001	Yes	Yes	No	No	Yes
1011/0726/005	Yes	Yes	No	No	Yes
1011/0726/006	Yes	Yes	No	No	Yes
1011/0726/007	Yes	Yes	No	No	Yes
1011/0726/008	Yes	Yes	No	No	Yes
1011/0607/009	Yes	Yes	No	No	Yes
1011/0726/001	Yes	Yes	No	No	Yes
1011/0726/004	Yes	Yes	No	No	Yes

Listing ... Listing of subjects randomized but not treated (Continued)

Study no./ Invest. no./ Subject no	Enrolled	Randomized	Treated	Safety evaluable	Excluded by FDA
Tonsillitis/pharyngitis					
[illegible]	Yes	Yes	No	No	No

Listing: Listing of subjects Treated but not safety evaluable

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	No post baseline safety assessment	Excluded by FDA
CAP						
3000/101/1361	Yes	Yes	Yes	No	Yes	No
3006/0012/035	Yes	Yes	Yes	No	Yes	No
3006/0060/016	Yes	Yes	Yes	No	Yes	No
3006/0425/005	Yes	Yes	Yes	No	Yes	No
3006/0008/034	Yes	Yes	Yes	No	Yes	No
3006/0054/005	Yes	Yes	Yes	No	Yes	No
3009/0243/008	Yes	Yes	Yes	No	Yes	No
3009/0337/003	Yes	Yes	Yes	No	Yes	No
3009/0357/003	Yes	Yes	Yes	No	Yes	No
3009/0298/011	Yes	Yes	Yes	No	Yes	No
3009/0326/010	Yes	Yes	Yes	No	Yes	No
3009/0349/001	Yes	Yes	Yes	No	Yes	No
3009 01/0362/101	Yes	Yes	Yes	No	Yes	No
3009 01/0366/102	Yes	Yes	Yes	No	Yes	No
3009 01/0368/115	Yes	Yes	Yes	No	Yes	No
3010/0490/001	Yes	Yes	Yes	No	Yes	No
3010/0490/004	Yes	Yes	Yes	No	Yes	No

BEST POSSIBLE COPY

Study no. / Invest. no. / Subject no.	Enrolled	Randomized	Treated	Safety evaluable	No post baseline safety assessment	Excluded by FDA
ABCB						
1003/0613/001	Yes	Yes	Yes	No	Yes	No
1007/0063/004	Yes	Yes	Yes	No	Yes	Yes
1007/0063/041	Yes	Yes	Yes	No	Yes	Yes
1007/0067/071	Yes	Yes	Yes	No	Yes	Yes
1007/0073/004	Yes	Yes	Yes	No	Yes	No
1007/0090/010	Yes	Yes	Yes	No	Yes	No
1007/0063/037	Yes	Yes	Yes	No	Yes	Yes
[illegible]/066	Yes	Yes	Yes	No	Yes	Yes
[illegible]/013	Yes	Yes	Yes	No	Yes	Yes
1007/0070/007	Yes	Yes	Yes	No	Yes	No
1007/0072/002	Yes	Yes	Yes	No	Yes	No
1007/0073/005	Yes	Yes	Yes	No	Yes	No
1007/0073/033	Yes	Yes	Yes	No	Yes	No
1007/0068/004	Yes	Yes	Yes	No	Yes	No
1007/0113/002	Yes	Yes	Yes	No	Yes	No

BEST POSSIBLE COPY

Study no / Invest no / Subject no.	Enrolled	Randomized	Treated	Safety evaluable	No post baseline safety assessment	Excluded by HGA
Sinusitis						
3002/1901/019	Yes	Yes	Yes	No	Yes	No
3002/2101/005	Yes	Yes	Yes	No	Yes	No
3002/2103/005	Yes	Yes	Yes	No	Yes	No
3005/0143/007	Yes	Yes	Yes	No	Yes	No
3005/0150/003	Yes	Yes	Yes	No	Yes	Yes
3005/0192/007	Yes	Yes	Yes	No	Yes	No
3005/0192/011	Yes	Yes	Yes	No	Yes	No
3005/0101/006	Yes	Yes	Yes	No	Yes	No
3005/0144/017	Yes	Yes	Yes	No	Yes	No
3005/0159/020	Yes	Yes	Yes	No	Yes	Yes
3005/0161/009	Yes	Yes	Yes	No	Yes	No
3005/0172/005	Yes	Yes	Yes	No	Yes	No
3005/0173/015	Yes	Yes	Yes	No	Yes	No
3005/0188/056	Yes	Yes	Yes	No	Yes	No
3005/0199/001	Yes	Yes	Yes	No	Yes	No
3011/0337/001	Yes	Yes	Yes	No	Yes	No

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Listing[illegible] Listing of subjects treated but not safety evaluable (Continued)

Study no./ Invest. no./ Subject no.	Enrolled	Randomized	Treated	Safety evaluable	No post baseline safety assessment	Excluded by FDA
Tonsillitis/pharyngitis						
3004/0406/002	Yes	Yes	Yes	No	Yes	No
3004/0604/001	Yes	Yes	Yes	No	Yes	No
3008/0234/005	Yes	Yes	Yes	No	Yes	No
3008/0260/004	Yes	Yes	Yes	No	Yes	No
3006/0264/001	Yes	Yes	Yes	No	Yes	No
3008/0235/302	Yes	Yes	Yes	No	Yes	No
3008/0245/301	Yes	Yes	Yes	No	Yes	No
3008/0249/202	Yes	Yes	Yes	No	Yes	No

BEST POSSIBLE COPY

Table 11.1.1.1.1 Number of subjects (%) with normal and high values alkaline phosphatase at pretherapy/entry and during treatment: HMR 1647 and comparator in LAP studies (EMR1647A/3001, HMR1647A/3004 and EMR1647A/3009, controlled; HMR1647A/3008, EMR1647A/3099 and HMR1647A/3010 uncontrolled) All subjects

Treatment group/ Pretherapy/entry status	During treatment (First pretherapy/entry through end of treatment + 7 days)									
	Normal		High							
	≤ULN		>ULN		>2ULN		>3ULN		>5ULN	
Controlled studies: HMR 1647										
Normal	406/431	(94.2)	24/431	(5.6)	0/431	(0.0)	1/431	(0.2)	0/431	(0.0)
High	39/67	(58.2)	41/67	(61.2)	7/67	(10.4)	1/67	(1.5)	0/67	(0.0)
Comparator										
Normal	396/426	(93.0)	28/426	(6.6)	1/426	(0.2)	0/426	(0.0)	0/426	(0.0)
High	33/68	(48.5)	45/68	(66.2)	6/68	(8.8)	3/68	(4.4)	1/68	(1.5)
Uncontrolled studies: HMR 1647										
Normal	687/724	(94.8)	37/724	(5.1)	0/724	(0.0)	0/724	(0.0)	0/724	(0.0)
High	19/118	(16.1)	81/118	(68.6)	10/118	(8.5)	4/118	(3.4)	2/118	(1.7)
									0/118	(0.0)

Note: ULN = upper limit of normal range (not extended normal range) for liver enzyme.
Normal: within normal range at baseline.
High : above normal range at baseline.

Table!!!!!!!!! Number of subjects (%) with normal and high values alkaline phosphatase at pretherapy/entry and during treatment: HMR 3647 and comparator in non-CAP studies(HMR3647A/3003, 3004, -3005, -3007, -3008 and HMR3647A/3011 controlled; HMR3647A/3002 uncontrolled) All subjects

Treatment group/ Pretherapy/entry status	During treatment (From pretherapy/entry through end of treatment + 7 days) Normal ≤ULN	High >1ULN	>2ULN	>3ULN	>5ULN	>8ULN
Controlled studies:						
HMR 3647						
Normal	1342/1364 (98.4)	22/1364 (1.6)	0/1364 (0.0)	0/1364 (0.0)	0/1364 (0.0)	0/1364 (0.0)
High	19/95 (20.0)	73/95 (76.8)	3/95 (1.1)	2/95 (2.1)	0/95 (0.0)	0/95 (0.0)
Comparator						
Normal	992/1010 (98.2)	19/1010 (1.8)	0/1010 (0.0)	0/1010 (0.0)	0/1010 (0.0)	0/1010 (0.0)
High	8/65 (12.3)	57/65 (87.7)	[illegible]/65 (0.0)	0/65 (0.0)	0/65 (0.0)	0/65 (0.0)
Uncontrolled studies:						
HMR 3647						
Normal	304/306 (99.3)	2/306 (0.7)	0/306 (0.0)	0/306 (0.0)	0/306 (0.0)	0/306 (0.0)
High	3/11 (27.3)	8/11 (72.7)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)

Note: ULN - upper limit of normal range (not extended normal range) for liver enzyme
Normal: within normal range at baseline
High : above normal range at baseline.

BEST POSSIBLE COPY

Table[illegible]: Number of subjects (%) with normal and high values total bilirubin at pretherapy/entry and during treatment: HMR 3647 and comparator in CAP studies (HMR3647A/3001, HMR3647A/3006 and HMR3647A/3009, controlled; HMR3647A/3000, HMR3647A/3099 and HMR3647A/3010 uncontrolled) - All subjects

Treatment group/ Pretherapy/entry status	During treatment (From pretherapy/entry through end of treatment + 7 days) Normal		High									
	<=ULN		>1ULN		>2ULN		>3ULN		>5ULN		>8ULN	
Controlled studies:												
HMR 3647												
Normal	444/452	(98.2)	8/452	(1.8)	0/452	(0.0)	0/452	(0.0)	0/452	(0.0)	0/452	(0.0)
High	28/32	(87.5)	4/32	(12.5)	0/32	(0.0)	0/32	(0.0)	0/32	(0.0)	0/32	(0.0)
Comparator												
Normal	428/432	(99.1)	3/432	(0.7)	0/432	(0.0)	0/432	(0.0)	1/432	(0.2)	0/432	(0.0)
High	32/42	(76.2)	9/42	(21.4)	1/42	(2.4)	0/42	(0.0)	0/42	(0.0)	0/42	(0.0)
Uncontrolled studies:												
HMR 3647												
Normal	688/701	(98.1)	12/701	(1.7)	0/701	(0.0)	1/701	(0.1)	0/701	(0.0)	0/701	(0.0)
High	53/62	(85.5)	6/62	(9.7)	3/62	(4.8)	0/62	(0.0)	0/62	(0.0)	0/62	(0.0)

Note: ULN : upper limit of normal range (not extended normal range) for liver enzyme.
Normal: within normal range at baseline.
High : above normal range at baseline.

Table!!!!!!!! Number of subjects (%) with normal and high values total bilirubin at pretherapy/entry and during treatment: HMR 3647 and comparator in non CAP studies(HMR3647A/3001, -3004, -3005, -3007, -3009 and HMR3647A/3011 controlled; HMR3647A/3002 uncontrolled) All subjects

Treatment group/ Pretherapy/entry status	During treatment (From pretherapy/entry through end of treatment + 7 days) Normal		High			
	<=ULN	>1ULN	>2ULN	>3ULN	>5ULN	>8ULN
Controlled studies: HMR 3647						
Normal	1326/1340 (98.4)	22/1340 (1.6)	0/1340 (0.0)	0/1340 (0.0)	0/1340 (0.0)	0/1340 (0.0)
High	21/37 (56.8)	14/37 (37.8)	1/37 (2.7)	1/37 (2.7)	0/37 (0.0)	0/37 (0.0)
Comparator						
Normal	991/997 (99.4)	6/997 (0.6)	0/997 (0.0)	0/997 (0.0)	0/997 (0.0)	0/997 (0.0)
High	33/41 (80.5)	7/41 (17.1)	1/41 (2.4)	0/41 (0.0)	0/41 (0.0)	0/41 (0.0)
Uncontrolled studies: HMR 3647						
Normal	287/295 (97.3)	8/295 (2.7)	0/295 (0.0)	0/295 (0.0)	0/295 (0.0)	0/295 (0.0)
High	0/3 (0.0)	3/3 (100)	0/3 (0.0)	0/3 (0.0)	0/3 (0.0)	0/3 (0.0)

Note: ULN = upper limit of normal range (not extended normal range) for liver enzyme.
Normal: within normal range at baseline.
High : above normal range at baseline.

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

/s/

Beth Duvall-Miller
4/17/01 11:27:40 AM
CSO
Final version of 3/15/01 telecon minutes
just sign off - edits have been incorporated

George Rochester
6/1/01 12:51:48 PM
BIOMETRICS

Edward Cox
6/8/01 04:06:53 PM
MEDICAL OFFICER

David Ross
6/11/01 03:37:19 PM
MEDICAL OFFICER

Joyce Korvick
7/31/01 01:46:15 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2001

To: —	**From:** Beth Duvall-Miller for Jose Cintron
Company: —	Division of Division of Anti-Infective Drug Products
Fax number: —	**Fax number:** (301) 827-2325
Phone number: —	**Phone number:** (301) 827-2125

Subject: request for regression analysis (Davidson) – CAP studies

Total no. of pages including cover: 2

Comments: Attached is Dr. Davidson's request for regression analysis

Document to be mailed: ☐ YES ☑ NO

Variables for a multivariate regression analysis to identify risk factors for PRSP in CAP

1. Demographics –
   -age
   -sex
   -weight
   -BMI
2. Medical history
   - COPD
   - recent history of Pneumonia
   - Asthma
   - Past history of TB
   - Diabetes mellitus
   - Renal (creatinine clearance ≤50mL/min)
   - Abnormal LFTs [YES= 1; No=0]
3. Smoking [Yes=1;No=0]
4. Prior of use of antimicrobials (within 7-14 days of enrollment)
5. History of recent hospitalization (within past six months or less)
6. Source (sputum , BAL, or blood) of resistant pathogens [bacteremic =1; nonbacteremic=0]
7. Genotype of resistant pathogen
8. Chest x-ray findings [single lobe=1; multiple lobes =2]
9. Geographic location [Country]
10. Facility [Outpatient/ home=1, Nursing home=2, Hospital= 3]
11. Severity of Infection- (Fine score)

Please submit the following to NDA 21-144:

1. Multivariate regression analysis

2. Datasets

3. Do this regression analysis with erythromycin-resistant *S. pneumoniae* in CAP as well using the same set of variables.

/s/

Beth Duvall-Miller
3/22/01 02:27:10 PM
CSO
This is the fax we sent on 3/22/01 - request for regression analysis
just sign off

Alma Davidson
3/29/01 04:58:46 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2001

To:	**From:** Beth Duvall-Miller for Jose Cintron
Company:	Division of Division of Anti-Infective Drug Products
Fax number:	**Fax number:** (301) 827-2325
Phone number:	**Phone number:** (301) 827-2125

Subject: request for Phase 1 analyses (Cox)

Total no. of pages including cover: 3

Comments: Attached are Dr. Cox's request for additional Phase 1 analyses

Document to be mailed: ☐ YES ☑ NO

Phase I Studies and Hepatic Abnormalities

I am trying to get a handle on the liver-related adverse events from the entire body of completed phase I studies. In the original NDA safety update, you had provided information such as the table on page 8:v251:p100, the information provided on pages 8:v251:p186-7, and their supporting tables. The key pieces of information that I am looking for can be summarized in the following tables A through C and by identifying the patient identification numbers (subjects number and study number). Would it be possible for Aventis to populate the following tables A through C using the entire database of completed phase I studies and also provide the patient identification numbers for the patients that populate each of the cells in Tables A and B?

Thank you.

Ed Cox

Table A. Frequency of Hepatic AEs per dosing* period for HMR 3647 – Phase I Single Dose Studies

Coded Term for Hepatic AE	**HMR 3647 Periods = N n/N**	**Placebo Periods = N n/N**
Liver Damage		
Increased AST		
Increased ALT		
Liver Function Test Abnormal		
Increased Alk. Phos.		
etc.		
etc.		

*Note: the unit of analysis is the dosing period

Table B. Frequency of Hepatic AEs per dosing* period for HMR 3647 – Phase I Multiple Dose Studies

Coded Term for Hepatic AE	**HMR 3647 Periods = N n/N**	**Placebo Periods = N n/N**
Liver Damage		
Increased AST		
Increased ALT		
Liver Function Test Abnormal		
Increased Alk. Phos.		
etc.		
etc.		

*Note: the unit of analysis is the dosing period

Table C. Frequency of Hepatic AEs in Single and Multiple Oral Dose Phase I Studies of HMR 3647 by Dose Level

		Single-Dose Studies				Multiple-Dose Studies		
HMR 3647 Dose (mg)		**Number of Hepatic AEs (n)**	**Number of Dosing Periods (N)**	**AEs/ Period (n/N) (%)**		**Number of Hepatic AEs (n)**	**Number of Dosing Periods (N)**	**AEs/ Period (n/N) (%)**
50								
100								
200								
400								
600								
800								
900								
1200								
1600								
2000								
2400								
Total								
Placebo								

"-" signifies no patients exposed to this dose

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

/s/

Beth Duvall-Miller
3/15/01 04:12:26 PM
CSO
Facsimile to Aventis for additional Phase 1 analyses [Cox]
just sign off

Edward Cox
3/27/01 03:48:23 PM
MEDICAL OFFICER

Joyce Korvick
5/7/01 08:45:15 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 28, 2000

To: —	**From:** Jose R. Cintron
Company: —	Division of Division of Anti-Infective Drug Products
Fax number: —	**Fax number:** 301-827-2326
Phone number: —	**Phone number:** (301) 827-2125

Subject: Discipline Review Completed for NDA 21-144 CMC Issues

Total no. of pages including cover: 5

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

List of Chemistry Deficiencies and Comments

Under: DESCRIPTION & CHARACTERISTICS FOR DRUG SUBSTANCE

Are there any differences in aqueous solubility between — — ? Does the lots tested for manufacturing the drug product contain any — . If so, do you detect any difference in dissolution?

Under: SYNTHESIS FOR DRUG SUBSTANCE

1. Please indicate how many batches, if any, of the drug substance (DS) used in formal stability batches were made from — material, — Are there any differences in impurity profile of the final drug substance prepared from these — sources?

2. In the discussion section of enodesclarithromycin and subsequent steps, HMR stated that it —

—

3. In the synthesis of HMR 3647, — you stated that in case of unsatisfactory purity, — Please describe the purity criteria or condition for implementing —

4. Please indicate how many batches, if any, of the drug substance (DS) used in formal stability batches were made from — Are there any differences in impurity profile of the final drug substance?

5. In the — / for synthesis of HMR 3647, please state the method used.

Under: REFERENCE STANDARD FOR DRUG SUBSTANCE

Please state the specifications for drug substance reference standards. If they are the same as the drug substance, you may reference them.

Under: SPECIFICATIONS AND TESTS FOR DRUG SUBSTANCE

Please explain why the acceptance range of the drug particle size is set between — — Is this a dissolution requirement?

Under: STABILITY FOR DRUG SUBSTANCE

Since the stability data provided is only — for the drug substance, there is no statistical basis to extrapolate a retest period to — Please propose an expiry date and update the NDA with — s stability data if available.

Please clarify the storage configuration of the (light sensitive) drug substance. It was stated that the drug was stored in — 4:v001:p119) during stability studies, but elsewhere in the TOC, it refers to a — for bulk packaging.

Under: METHODS OF MANUFACTURING AND PACKAGING FOR DRUG PRODUCT

Please provide a description of the — s if you intend to — Ketek tablets.

Under: SPECIFICATIONS AND METHODS FOR DRUG PRODUCT

1. **Please state the page reference of the regulatory identification LC method, — or — was not found in the validation or method section. The identification codes in the validation section in volume 4:V005:p056 (— and 4:V005:p106 (— , appear to start with coded with — apparently due to regional difference. Please confirm whether they are related to methods cited in the regulatory specification.**

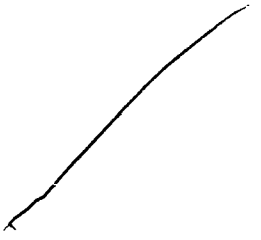
2. **Please state the page reference of the LC method for degradation product, — was found in Volume 8, page 084, in the validation or method section but — was not found anywhere. Are — equivalent to — the regulatory method? If they are different, please state the — condition (please refer also to related comments in method validation section).**

3. **On page 4:v005:p021, under HMR3647 400 mg, film-coated tablets - Specifications and analytical procedures, presumably proposed for the US, another set of specification/method mostly similar is proposed on 4:v008:p080, the latter include studies for other countries. Please confirm that the US regulatory specifications for the product are those listed under 4:v005: p021.**

4. **On page 4:v005:p021, under HMR3647 400 mg, film-coated tablets - Specifications and analytical procedures , under uniformity of dosage form, please add : USP <905> requirement will be met.**

Under: METHOD VALIDATION

1. There were some confusion reported from the FDA laboratory in determining which — was actually used for analysis. It was stated on page 33 and page 31(Volume 4 of NDA) under



2. On Page 56/Volume 8, under document — , HPLC method for related substances, the — . Is this correct? Is this similar to the regulatory method with a different reference code?

3.

, within HPLC method guidance, a range of operation parameters that is appropriate for this method and explain the difficulty experienced in reproducing the method.

4. Under Appendix A.13, HMR 3647 - Validation of analytical procedures, HMR 3647 - Validation of analytical procedures - HPLC procedure for estimation of related substances, Document — (4:v004:p004), please state whether this procedure is for drug substance or drug product, and explain why this method is not listed under regulatory specification/methods of either.

5. Under Appendix A.13, HMR 3647 - Validation of analytical procedures, HMR 3647 - Validation of analytical procedures - HPLC procedure for assay Determination, Document — (4:v004:p058), please clarify whether this procedure is a method for drug substance (4:V001:p128) or drug product. It appears not referenced under regulatory specification of either.

Under: STABILITY FOR DRUG PRODUCT

1. Since the stability data provided is only — for the drug product, there is no statistical basis to extrapolate a retest period to — Please update with — stability if available.

2. **The sponsor recommends that the drug substance should be protected from light; however, no such recommendation was made during the discussion for the Ketek tablet stability. However, on the package label , please explain.**

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-144	Efficacy Supplement Type	Supplement Number
Drug: Ketek™ (telithromycin)	Applicant: Aventis Pharmaceuticals	
RPM: Judit Milstein	HFD-520	Phone # 301-827-2207
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1 (NME)
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	April 16, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-January 24, 2003 AE-June 1, 2001
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ? ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS March 4, 2004/October 22, 2002 OPDRA August 28, 2000 DDMAC PI- March 5, 2004 DDMAC PPI-February 27, 2004 ODS/DSRCS-March 11, 2004 DSRCS December 16, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See in action letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	March 11, 2002

• Pre-Approval Safety Conference (indicate date; approvals only)	X
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	April 26, 2001 January 8, 2003
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	April 1, 2004 February 16, 2004
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Post Marketing- 3-31-04 February 27, 2004 March 23, 2003 March 20, 2003 August 22, 2001 March 3, 2003 February 27, 2001 March 31-04 March31-04 September 14, 2001 ODS safety 3-30-04
Microbiology (efficacy) review(s) *(indicate date for each review)*	3-31-04 October 31, 2003 November 1, 2002 December 27, 2000
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MO review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	3-31-04 December 20, 2002 June 4, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	March 31, 2004 January 29, 2003 May 31, 2001
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	3-30-04 January 21, 2003 September 14, 2000
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	March 31, 2004 November 29, 2000 February 27, 2001 January 16, 2003 March 2, 2004
Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	November 29, 2000
• Review & FONSI *(indicate date of review)*	

• Review & Environmental Impact Statement *(indicate date of each review)*	
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: March 1, 2004 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	January 22, 2000 June 30, 2000 March 19, 2001 January 21, 2001
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A