

Appendix C



NDA 21-144

Aventis Pharmaceuticals Inc
Attention: Gillian Ivers-Read, B.Sc.
Vice President
Global Drug Regulatory Affairs
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Ms. Ivers-Read:

Please refer to your new drug application (NDA) dated February 28, 2000, received March 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KETEK™ (telithromycin) 400 mg. Please note that for administrative purposes, we have assigned a new NDA number (NDA 21-391) to the Tonsillitis/Pharyngitis indication. Our response to this proposed indication is addressed in a separate letter.

We acknowledge receipt of your submissions dated:

March 23, 2000	April 5, 200	April 11,2000	April 13, 2000	April 14, 2000
April 20, 2000	May 4, 2000	June 1, 2000	June 2, 2000	June 21, 2000
June 22, 2000	June 29, 2000	June 30, 2000	July 5, 2000	July 6, 2000
July 10, 2000-2	July 13, 2000	July 19, 2000	July 21, 2000	July 28, 2000
August 4, 2000	August 7, 2000-2	August 8, 2000	August 11, 2000	August 12, 2000
August 16, 2000	August 24, 2000	August 29, 2000	August 30, 2000	August 31,2000-2
Sept. 1, 2000-2	Sept. 7, 2000	Sept. 8, 2000	Sept. 11, 2000	Sept. 13, 2000
Sept. 14, 2000	Sept. 19, 2000-2	Sept. 20, 2000-2	Sept. 28, 2000	Sept. 29, 2000-2
October 2, 2000	October 3, 2000	October 4, 2000	October 6, 2000	October 19, 2000
October 20, 2000-2	October 23, 2000	October 24, 2000	October 25,2000	October 27, 2000
October 31, 2000-2	Nov. 2, 2000-2	Nov. 3, 2000-2	Nov.7, 2000	Nov. 8, 2000
Nov. 13, 2000	Nov. 15, 2000	Nov. 16, 2000-2	Nov. 17, 2000	Nov. 20, 2000
Nov. 28, 2000	Nov. 29, 2000	Nov. 30, 2000	Dec. 1, 2000	Dec. 4, 2000
Dec. 5, 2000-2	Dec. 7, 2000	Dec. 12, 2000	Dec. 14, 2000	Dec. 18, 2000
Dec. 20, 2000	Dec. 21, 2000-2	January 3, 2001	January 4, 2001-2	January 10, 2001
January 12, 2001	January 17, 2001	January 19, 2001(2)	January 22, 2001	January 24, 2001
January 25, 2001	January 26, 2001	January 31, 2001	February 1, 2001	February 7, 2001
February 14, 2001	February 15, 2001	February 16, 2001-2	February 20, 2001-3	February 21, 2001
February 26, 2001	February 27, 2001-2	February 28, 2001	March 1, 2001	March 2, 2001
March 9, 2001	March 12, 2001	March 16, 2001-2	March 19, 2001	March 20, 2001-2
March 21, 2001-4	March 22, 2001	March 23, 2001-2	March 24, 2001	March 28, 2001
March 29, 2001-3	April 3, 2001-2	April 4, 2001	April 6, 2001	April 10, 2001
April 17, 2001-2	April 18, 2001	April 20, 2001	April 27, 2001-2	May 1, 2001
May 24, 2001				

We have completed the review of this application for Community-Acquired Pneumonia (CAP), Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB), and Acute Bacterial Sinusitis (ABS), as amended, and it is approvable. However, the data are insufficient in your NDA to assess fully the potential risks posed by the concentration-related effect of telithromycin on cardiac repolarization, hepatotoxicity, and drug exposure in patients with renal and/or hepatic impairment. Finally, the differences in the cause of mortality in the telithromycin treatment groups versus comparators are of concern.

Before this application may be approved, it will be necessary for you to address the following:

Clinical Studies Targeting Resistant Pathogens

You should conduct a large clinical study of CAP/ABS in order to capture further patients with *S. pneumoniae* isolates resistant to penicillin and/or erythromycin, and beta-lactamase producing strains of *H. influenzae*. Within this large database, monitoring and analysis of adverse event reports, including hepatic, cardiac (QT interval) and visual adverse events, are highly recommended in order to obtain a larger safety database upon which to assess the benefit/risk profile.

- Penicillin-resistant *S. pneumoniae* (PRSP) and erythromycin-resistant *S. pneumoniae* (ERSP): Based on our review of the clinical data submitted in your NDA, we have concluded that insufficient data were provided for the treatment of community-acquired pneumonia (CAP) of mild to moderate severity and acute bacterial sinusitis (ABS) due to PRSP and ERSP.
- Acute Bacterial Sinusitis (ABS): Before we would be prepared to approve a PRSP or ERSP claim for ABS, you should establish clinical efficacy of telithromycin against PRSP in a more serious indication (e.g., CAP).

Safety and Clinical Pharmacology:

1. It would be helpful to conduct a phase III study of CAP/ABECB/ABS to assess further adverse events associated with telithromycin, particularly in patients at increased risk for potential drug-related toxicity. Such a study should be randomized, with at least 35% of the recruited study population consisting of patients 50 years of age and older. Exclusion criteria regarding concomitant medications should be minimized. Recruitment of patients with renal and/or hepatic impairment is encouraged. This study should include the monitoring and analysis of all adverse events, with particular attention to hepatic, visual, cardiovascular, and vasculitic adverse events. Investigations of any mortality outcomes by investigators should be conducted to evaluate optimally possible cardiac or liver toxicities or evidence of systemic vasculitis.
2. Investigate the steady-state pharmacokinetics of telithromycin following administration of 400 mg, 600 mg and 800 mg once daily to patients with mild, moderate, and severe renal impairment in order to provide dose adjustment recommendations for the product label. Blood should be sampled at multiple time-points to assay for telithromycin. Electrocardiograms should be obtained at the time of each blood sample and analysis of changes in QT interval duration performed.
3. Investigate the effect of co-administration of ketoconazole on the steady-state pharmacokinetics

of telithromycin following administration of 800 mg once daily to elderly patients with mild to moderate renal impairment. This information is necessary to characterize drug exposure in patients at potentially greater risk due to multiple perturbations of drug elimination pathways. Blood should be sampled at multiple time-points to assay for telithromycin. Electrocardiograms should be obtained at the time of each blood sample and analysis of changes in QT interval duration performed.

4. Conduct an *in vitro* study (or studies) to investigate the drug metabolism of RU 76363 including an assessment of the potential effect of RU 76363 on IKr. Telithromycin and some other anti-infectives should be used as comparators (e.g., clarithromycin, moxifloxacin, and levofloxacin).
5. The visual blurring reported in the clinical studies is not currently well understood or adequately studied. It may be a signal for a more serious condition such as angle closure glaucoma or retinal toxicity. Additional clinical studies are recommended to address telithromycin's effect on visual acuity, refraction, accommodation, anterior chamber angle, lens, pupil dilation, tear film stability, visual field (threshold automated testing), and color vision.

General Comments:

1. Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB): Your current application regarding *H. influenza* and *M. catarrhalis* is insufficient due to low numbers of isolates.

Please note that revised draft labeling is not being provided at this time. Further revisions to the submitted label will be required before this application can be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA, may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jose R. Cintron, R.Ph., M.A., Sr. Regulatory Management Officer/Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Dianne Murphy
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