CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

ADMINISTRATIVE DOCUMENTS

13/14. PATENT INFORMATION/CERTIFICATION

Patent Number:	United States Patent No. 5,635,485
Expiration Date:	April 21, 2015
Patent Owner:	Aventis Pharma, SA 20, Avenue Raymond Aron 92 165 Antony Cedex, France
Type of Patent:	Drug Product Patent Drug Substance Patent Method of use

Patent Number:	United States Patent No. 5,527,780
Expiration Date:	November 1, 2013
Patent Owner:	Aventis Pharma, SA 20, Avenue Raymond Aron 92 165 Antony Cedex, France
Type of Patent:	Drug Product Patent Drug Substance Patent Method of use

The undersigned also declares that United States Patent No. 5,635,485 and United States Patent No. 5,527,780 cover HMR3647 (telithromycin), the drug substance of the product for which NDA 21-144 was submitted for approval on February 28, 2000, as well as any composition or method of use which employs said drug substance.

This declaration is submitted herewith. Please list the No. 5,635,485 and No. 5,527,780 patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

Steve Caffé, M.D.
Vice President, US Regulatory Affairs
Aventis Pharmaceuticals Inc.

8 JUL 02
Date

17. FIELD COPY CERTIFICATION

In accordance with 21CFR 314.50(l)(3), a true copy of the Chemistry section (Item 4) of this amendment to NDA 21-144 is being submitted concurrently with this submission to the following address:

Charles Sedgwick, District Director
Kansas City District Office
Food and Drug Administration
11510 West 80th St.
Lenexa, KS 66214-3338

Steve Caffé, M.D.
Vice President, US Regulatory Affairs
Aventis Pharmaceuticals Inc.

8 JUL 02
Date

16. DEBARMENT CERTIFICATION

Aventis Pharmaceuticals Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

J. Michael Nicholas, Ph.D.
Vice President, US Regulatory Affairs
Marketed Products
Aventis Pharmaceuticals Inc.

2/22/00
Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-144 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: March 1st, 2000 Action Date: April 1, 2004

HFD 520 Trade and generic names/dosage form: Ketek™ (telithromycin) Tablets, 400 mg

Applicant: Aventis Pharmaceuticals Therapeutic Class: Ketolide Antibiotic

Indication(s) previously approved: none

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

Number of indications for this application(s): 3

Indication #1: Acute bacterial exacerbation of chronic bronchitis

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

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

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

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Bacterial Sinusitis

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

☐ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ___Partial Waiver _X_Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**< yr.** 18	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other: Need safety information in adults before proceeding with pediatrics the sponsor will submit a PPSR in the near future**

Date studies are due (mm/dd/yy): March 31, 2008

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

Indication #3: Community-acquired pneumonia

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

- ☐ **Yes: Please proceed to Section A.**

- **X No: Please check all that apply: ___Partial Waiver _X_Deferred ___Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ < yr. 18____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other: Need safety information in adults before proceeding with pediatrics the sponsor will submit a PPSR in the near future**

Date studies are due (mm/dd/yy): March 31, 2008

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

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-144
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Judit Milstein
4/14/04 02:59:03 PM
CSO

John Alexander
4/15/04 09:45:51 AM
MEDICAL OFFICER

EXCLUSIVITY SUMMARY for NDA # 21-144 SUPPL #
Trade Name Ketek Generic Name: telithromycin

Applicant Name: Aventis Pharmaceuticals HFD- 520

Approval Date: March 31, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/X/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X/

   If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
4/13/04 03:25:19 PM
CSO

Frances LeSane
4/13/04 04:23:05 PM
CSO

Lillian Gavrilovich
4/14/04 02:58:47 PM
MEDICAL OFFICER

Office/Division Memorandum for NDA 21-144 Ketek™ (Telithromycin)

The Division of Anti-Infective Drug Products/Office of Drug Evaluation 4 will approve the new drug application (NDA) for Ketek™ (telithromycin) Tablets for the treatment of adults with respiratory tract infections, including community-acquired pneumonia, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis. The approval includes treatment of patients with pneumonia due to multi-drug resistant *Streptococcus pneumoniae.* Ketek, a member of the ketolide class of antibiotics, was submitted as an NDA in March, 2000 by Aventis Pharmaceuticals, Inc. The Agency concluded that while efficacy was generally demonstrated, significant safety concerns existed, and too few patients had infections with resistant bacteria to permit an overall risk-benefit assessment. Safety problems included potential liver toxicity, QT prolongation with potential cardiac arrythmias, drug-drug interactions, and visual side effects. At an Advisory Committee meeting in April, 2001, AC members recommended additional studies to delineate the drug's safety profile and to gain experience with patients with pneumonia due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP). Aventis conducted these additional studies during 2001-2002, including a large controlled safety trial in a usual care setting in outpatients with respiratory tract infections (referred to hereafter as study 3014). Review of study 3014 was complicated by systematic failure of the trial monitoring program to detect data integrity problems when they clearly existed, making it difficult to rely on this study to support a regulatory action. When Aventis resubmitted the NDA in October, 2003, our understanding of the overall risk-benefit profile of Ketek was greatly enhanced by information from spontaneous adverse event reports for — prescriptions in Europe and Latin America.

Summary of Key Information and Actions

- In March, 2000, Aventis submitted the NDA for Ketek for treatment of respiratory tract infections in adults, seeking approval for four indications (community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and pharyngitis), including a claim for drug-resistant *Streptococcus pneumoniae.* Few data were submitted on patients with infections due to resistant bacteria at this time.
- The Agency discussed the Ketek NDA at an April, 2001 Advisory Committee meeting, concluding that clinical trials revealed similar efficacy for Ketek and comparator antimicrobial drugs (except for pharyngitis, where substantial evidence of efficacy was not demonstrated). But safety concerns led Advisory members and the Agency to ask for additional safety and efficacy data. The Agency issued an approvable letter in June, 2001.
- Safety information in animals and man led to three main concerns: hepatic, cardiac (increased QT interval and drug-drug interactions), and visual side effects. In patients treated with Ketek, a cluster of liver enzyme elevations occurred in elderly patients, and a case of biopsy-confirmed eosinophilic hepatitis was consistent with a drug-induced liver injury.
- Aventis submitted additional efficacy and safety studies in July, 2002, including study 3014, a 24,000 patient usual care study in mild respiratory infections. As noted above, inspections of this study raised questions regarding trial monitoring to detect data integrity problems.
- Aventis responded to a January, 2003 approvable letter with additional information, to clarify the conduct of study 3014 and to analyze substantial post-marketing experience with safety data for — prescriptions in Europe and South America.

Summary of Agency Actions and Advisory Recommendations for Ketek

Review of the original NDA raised significant safety concerns, including:

- Potential telithromycin hepatotoxicity, based on toxicologic studies, a cluster of transaminase elevations in elderly telithromycin-treated patients, and a case of biopsy-confirmed eosinophilic hepatitis in a telithromycin-treated patient.
- Potential CYP 3A4-mediated drug interactions, including QT prolongation.
- Telithromycin-related visual blurring.
- Few data on patients with co-morbidities or receiving potentially interacting drugs.
- The implications of these factors in light of anticipated broad population exposure.

These issues were discussed in an April, 2001 Anti-Infective Drugs Advisory Committee meeting. The Committee voted against approval and recommended more studies to demonstrate efficacy in patients with resistant *S. pneumoniae*, as well as more safety data, to characterize more fully the benefit/risk of telithromycin in the broad population, including patients with co-morbidities or receiving potentially interacting medications. The Agency subsequently issued an approvable letter which requested this additional information.

Study 3014, a large controlled usual care trial in approximately 24,000 patients with mild respiratory tract infections, was designed to address the need for additional safety information by examining potential toxicities of telithromycin with regard to hepatic, cardiac, and visual adverse events. Additional clinical pharmacology studies were also to be conducted to address the visual effects, and examine the pharmacokinetics and electrophysiologic effects of telithromycin in subjects with impaired clearance.

Aventis submitted the requested studies in July, 2002. The Agency convened a second Advisory Committee meeting in January, 2003, and the Committee judged that safety and efficacy for the requested indications had been demonstrated, in large measure on the basis of study 3014. Presentation to the Advisory Committee, however, did not include a discussion of serious data integrity issues uncovered in this large usual care study by Agency inspections. Since description of the risk profile of telithromycin and assessment of its risk-benefit ratio (particularly with regard to hepatic and visual toxicities) rested heavily on this large safety study, the Agency issued a second approvable letter in order to better understand how study 3014 was conducted. The October, 2003 submission addressed issues of study 3014 conduct, and included as well post-marketing reports for spontaneous adverse events for approximately —→ prescriptions for patients in foreign countries. The conduct of study 3014, including systematic problems with its monitoring, led to questions regarding what role this study could play in determining regulatory action. However, the Agency was able to rely on the post-marketing experience to conclude there was substantial evidence of safety.

Summary of Overall Safety

Agency reviewers have done a very thorough analysis of pre-clinical and clinical safety data, including evaluation of spontaneous post-marketing reports for [redacted] prescriptions overseas. Animal studies showed significant toxic effects of telithromycin on the liver in multiple species (mice, rats, dogs and monkeys), as manifested by increased liver-associated enzymes, increased total bilirubin, hepatic necrosis and associated inflammation, and phospholipidosis. In comparing these effects in animals given telithromycin or clarithromycin, it was noted that the hepatotoxic effects of telithromycin appeared greater. Telithromycin elicited delayed cardiac repolarization *in vitro* in animal and human cells, and *in vivo* in animals. In the dog, telithromycin caused a markedly increased heart rate and increased QT interval (27-30 milliseconds). In a comparative animal study, clarithromycin and erythromycin each increased the QT interval by 17 milliseconds; telithromycin, by 30 msec.

Human exposure showed that telithromycin concentrations in plasma are highly variable [redacted] after a single dose, up to [redacted] after multiple doses). Telithromycin is a CYP 3A4 and 2D6 substrate, as well as a strong CYP3A4 inhibitor. It is primarily metabolized and eliminated by the liver. In subjects with liver impairment, the half-life of telithromycin significantly increased, as did the role of renal elimination.

Safety information in man led to the following main areas of concern: hepatic effects, visual complaints, potential CYP 3A4-mediated drug-drug interactions, and QT prolongation. Data collected from Phase 1-3 studies, from study 3014 in a usual care setting, and post-marketing exposures in approximately [redacted] patients are summarized below for each area of concern.

Hepatic effects

In Phase 1 studies, 8 elderly subjects received a single 2 gram dose of telithromycin; 3 patients had elevated liver transaminase values (ALT and AST levels ranging from 100-300, ALT > AST). Phase 1 data showed no clear dose-response for hepatic adverse events. In Phase 3 studies, 2 patients experienced serious hepatic adverse events possibly associated with telithromycin. One patient underwent a liver biopsy, read by Agency consultants as consistent with drug-induced liver injury. A second biopsy nine months later was consistent with autoimmune hepatitis, possibly resulting from neoantigen exposure after drug injury. The observed rate of possibly drug-related serious hepatic adverse events in Phase 3 trials was 2/4472 (0.0004%, 95% CI [0.0001, 0.0017]). Analyses of liver function tests from the comparative Phase 3 community-acquired pneumonia (CAP) studies in patients who were normal at baseline showed a greater proportion of patients with low to moderate elevations (1-2x ULN, 2-3x ULN, and 3-5x ULN) of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the telithromycin-treated patients than in comparator-treated patients. The AST and ALT elevations from patients in CAP studies were present during the On-Therapy and Post-Therapy visits. While infrequent, concomitant transaminase and total bilirubin elevations were only found

in telithromycin-treated patients and were categorized as low level elevations between 1x and 2x the upper limit of normal (ULN).

Study 3014 was a large controlled outpatient safety study of adults with mild respiratory tract infections. Over 24,000 patients were enrolled and received either telithromycin or amoxicillin/clavulanic acid; the latter agent is a recognized cause of cholestatic hepatitis. Analyses of liver function tests in study 3014 showed a higher rate of high (>8x ULN) transaminase elevations in telithromycin-treated patients compared to amoxicillin/ clavulanic acid-treated patients. In addition, there was a higher incidence of such elevations in patients receiving 7 to 10 days of telithromycin compared to patients receiving 5 days of telithromycin. There were five patients (three telithromycin and two amoxicillin-clavulanic acid) with confirmed hepatic endpoints (hepatic adverse events possibly related to study drug), as adjudicated by the study's Clinical Evaluation Committee (CEC). The Agency medical reviewer agreed with the CEC's assessment of these cases. One telithromycin-treated patient in this group had a liver biopsy performed which showed cholestasis and "rare red dead hepatocytes"; however, the biopsy was performed more than three weeks after telithromycin treatment had ended. The Agency's pathology consultant assessed this biopsy as showing possible evidence of drug injury. The Agency reviewer assessed one other telithromycin-treated patient as having a possibly drug-related hepatic adverse event.

As of October, 2003, with [redacted] prescriptions written in Europe and Latin America, there were 90 reported telithromycin-associated hepatic adverse events reported by 43 different patients. As is usually the case with spontaneous post-marketing reports, the majority of these lacked sufficient detail to assess causality or liver injury pattern. For those reports which did contain sufficient data, a cholestatic pattern of injury was most common. The pattern resembled a hepatocanalicular injury, well described in patients treated with erythromycins. There were less common reports of cytolytic injury. One death was reported due to a hepatic adverse reaction. This complex patient was felt to have had acute hepatitis A, possible Q fever, and high dose acetaminophen consumption. Although it is difficult to determine accurate incidence rates of adverse events based on post-marketing data, the number and severity of the telithromycin-related reports appear similar to erythromycins. As summarized by FDA consultant Dr. William Lee in comments to the January, 2003 Anti-Infective Advisory Committee, telithromycin is clearly hepatotoxic, but the data collected thus far suggest that it is not significantly more hepatotoxic than marketed macrolides, and relative differences in toxicity between telithromycin and macrolides may only become evident during further post-marketing surveillance.

Visual effects

In placebo-controlled Phase 1 studies, patients under 40 years of age received a single 2400 mg dose of telithromycin. The incidence of blurred vision ranged from 27% to 83%. In older patients given 2400 mg, the incidence of blurred vision ranged from 0% to 33%. Blurry vision developed 1 to 3 hours after dosing and lasted up to 20 hours. Thorough ophthalmologic examinations during the occurrence of blurry vision did not reveal any significant change from baseline. The effect was described as a difficulty focusing at a far distance, without any change in intraocular pressure, anterior chamber angle, modification of the visual field, color vision, or fundus. Blurred vision was associated in one case with a reduced near visual acuity, and in 2 cases with a reduced amplitude of accommodation, but not associated with alteration of far visual acuity, refraction, or tear film. The mechanism of telithromycin-induced visual blurring appears related to a delay in accommodation, but this does not explain the finding in older patients, who have decreased accommodative ability and who should therefore be less affected by telithromycin.

In Phase 3 studies, the incidence of visual adverse events in Ketek-treated patients in all controlled Phase 3 studies (excluding study 3014) was 26/2702 (1.0%) and was 4/2139 (0.2%) among comparator-treated patients. Women were more likely to have visual adverse events during Ketek treatment than were men (1.4% vs 0.5%). Of Ketek-treated patients developing blurred vision, 16/20 (80%) were 40 or younger. The mean duration of blurry vision in these studies was 3.3 days (range, 1 – 10 days). Of note, in Ketek-treated patients receiving a concomitant CYP 3A4 inhibitor in Phase 3 trials, the incidence of blurry vision was almost 5 times that in patients not receiving a 3A4 inhibitor (1.9% vs. 0.4%).

Both study 3014 and post-marketing reports add further descriptive information to our understanding of Ketek-associated visual adverse events and their impact on daily activities. In Study 3014, 74 of approximately 12,000 Ketek-treated patients had a confirmed visual endpoint. Of those with blurred vision, 33% of Ketek-treated patients reported a significant impact on activities; of the 17 patients where a specific comment was included, 7 had difficulty reading, 5 were unable to work and one of these was also unable to drive, a further 4 were also unable to drive, and one was unable to baby-sit.

In the post-marketing database of approximately — exposures as of October, 2003, there were 414 telithromycin-associated visual adverse events reported by 316 patients. More events occurred in younger, female patients. Adverse events referable to vision were the most common post-marketing signal and comprised 34% (316/937) of all patients with any reported post-marketing complaint. Some of these patients treated with Ketek described significant disability/incapacity as a result of visual blurring. The majority of these cases were temporary, lasting on the order of hours to a few days. Onset of visual adverse events in the post-marketing database was not predictable, occurred at any time during treatment, and did not show permanent effects albeit in incomplete reports. For patients who experience visual problems, the Ketek package insert states

that patients should not drive or engage in hazardous activities. Additional information will be provided in a Phase 4 commitment to further characterize visual complaints.

QT effects, drug-drug interactions, and special populations

Telithromycin has an effect on cardiac repolarization which is considered concentration dependent. When telithromycin is administered alone, the effect on prolongation of QT appears to be modest. Based on data from Phase 3 studies, telithromycin is associated with a mean on-therapy increase of QTc (Bazett's formula) of 1.5 msec and a mean on-therapy increase of QTc (Fridericia's formula) of 3.8 msec. Phase 3 data did not indicate that the QT effects of telithromycin were substantially different from similar drugs in the macrolide class.

In controlled Phase 1 trials, when subjects with multiple perturbations (such as renal impairment and co-administration of ketoconazole) were studied, effects on cardiac repolarization were not substantially worsened. There were no cardiac adverse events noted and no outliers for EKG assessments (QTc $\geq$ 450 msec for men; $\geq$ 470 msec, for women; absolute change $\geq$ 60 msec).

Drug-drug interaction studies have shown that telithromycin is a strong CYP3A4 inhibitor. When Ketek is given together with simvastatin, the plasma levels of simvastatin and its active metabolite were significantly increased by 8-15 fold. Since there is dose-dependent risk of myopathy with statins, the package insert for Ketek states that therapy with statins that are metabolized by CYP3A4 (such as simvastatin, lovastatin, and atorvastatin) should be interrupted when Ketek is prescribed. Additionally, the package insert contraindicates co-administration of Ketek with cisapride and pimozide, two drugs known to have clinically significant effects on cardiac repolarization.

In a careful review of post-marketing data, there were a total of 101 cardiac adverse events reported by 86 patients. The majority of these events were either cardiac events occurring in older patients with pre-existing cardiac disease or symptoms, such as palpitations or tachycardia, occurring as part of a non-cardiac multi-symptom event. QT interval prolongation often results in cardiac events outside the setting of the type of medical monitoring necessary to identify them, and because these events may degenerate into non-distinct ventricular fibrillation, it is often difficult to identify potential drug-related QT toxicity in the post-marketing setting. Despite these limitations, review of these post-marketing data does not indicate any unusual cardiac safety signal for telithromycin.

Exposure to telithromycin is doubled in patients with severe renal impairment (creatinine clearance less than 30 mL/min) following multiple doses of 800 mg. With mild to moderate renal impairment, no significant change in telithromycin exposure was noted, and no dosage adjustment is needed. For patients with severe renal compromise, a 600 mg daily dose appears to be optimal, but a formulation for this dose does not currently exist in the U.S.

Summary Overall Efficacy

The Ketek NDA included studies in four indications: Acute Bacterial Exacerbation of Chronic Bronchitis (AECB), Acute Bacterial Sinusitis (ABS), Community-Acquired Pneumonia (CAP), and Tonsillitis/Pharyngitis (T/P). Data submitted in support of these claims are described for each indication. The T/P indication was not approved. Most of the studies supporting the efficacy of the product were submitted in the original NDA. The resubmission included two controlled studies (1 CAP, 1 AECB) and an open label CAP study. The 3rd submission provided some re-analyses of pathogen-specific outcomes and an evaluation of the data supporting the claim for CAP due to Multi-Drug Resistant *Streptococcus pneumoniae* (MDRSP).

Acute Bacterial Exacerbation of Chronic Bronchitis

Two studies (3003 and 3007) of AECB were submitted with the original NDA. One study (3013) was submitted in the NDA resubmission. The studies were similar in design, comparing telithromycin 800 mg daily for 5 days with 10 days of comparator treatment. The results for the three studies are summarized in the following table.

Clinical Outcomes at Test-of-Cure in AECB Studies

	Telithromycin				Comparators				2-sided 95% Confidence Interval
	Regimen	N	Cure	%	Regimen	N	Cure	%	
PPc Population									
Study 3003	TEL 5 d	115	99	86.1	AMC 10 d	112	92	82.1	(-6.4%, 14.3%)
Study 3007	TEL 5 d	140	121	86.4	CXM 10 d	142	118	83.1	(-5.8%, 12.4%)
Study 3013	TEL 5 d	225	193	85.8	CLA 10 d	231	206	89.2	(-9.9%, 3.1%)
MITT Population									
Study 3003	TEL 5 d	160	130	81.3	AMC 10 d	160	125	78.1	(-6.3%, 12.6%)
Study 3007	TEL 5 d	182	142	78.0	CXM 10 d	191	138	72.3	(-3.5%, 15.1%)
Study 3013	TEL 5 d	270	224	83.0	CLA 10 d	282	236	83.7	(-7.3%, 5.9%)

PPc = Clinical Per-protocol Population, MITT = Modified Intent-to-treat Population
TEL = telithromycin, AMC = amoxicillin/clavulanate, CXM = cefuroxime axetil, CLA = clarithromycin,
Confidence interval is for the difference of the two cure rates.

The results of studies 3003 and 3007 supported the approvability of telithromycin for the treatment of acute exacerbations of chronic bronchitis. However, concerns were raised about the activity of telithromycin against *Haemophilus influenzae*. In study 3003, clinical cure was reported in 8/14 (57.1%) of telithromycin-treated patients with AECB due to *H. influenzae*, compared to 10/12 (83.3%) treated with amoxicillin/clavulanate. In study 3007, cure rates for AECB patients with *H. influenzae* were 9/11 (81.8%) for telithromycin patients and 3/5 for cefuroxime axetil patients. Study 3013 was provided in the NDA resubmission to provide greater experience with telithromycin treatment of AECB patients with *H. influenzae*. The pathogen-specific cure rates were 27/35 (77.1%)

for telithromycin patients and 32/36 (88.9%) for clarithromycin patients. The following two tables show the pathogen-specific cure rates for AECB patients in the modified intent-to-treat (MITT) and per protocol (PP) populations, respectively. The tables combine clinical outcomes by pathogen from all three clinical trials. All telithromycin-treated patients received 800 mg once daily for 5 days.

Pathogen-Specific AECB cure rates in the MITT population

Organism	Telithromycin	Comparator
S. pneumoniae	82.8% (24/29)	79.2% (19/24)
H. influenzae	73.1% (57/78)	70.8% (51/72)
M. catarrhalis	90.9% (30/33)	80.5% (33/41)

Pathogen-Specific AECB cure rates in the PP population

Organism	Telithromycin	Comparator
S. pneumoniae	81.5% (22/27)	78.9% (15/19)
H. influenzae	73.3% (44/60)	84.9% (45/53)
M. catarrhalis	93.1% (27/29)	85.3% (29/34)

Though the clinical cure rate for telithromycin-treated patients with AECB due to *H. influenzae* was somewhat lower than for comparator patients in the per protocol population, the rates were similar in the MITT population. Cure rates for patients with *S. pneumoniae* and *M. catarrhalis* were similar across treatment arms. These data provide substantial evidence of efficacy of telithromycin (800 mg once daily for 5 days) for the treatment of AECB.

Acute Bacterial Sinusitis

Three studies of telithromycin for the treatment of acute bacterial sinusitis (ABS) were performed. All three studies were submitted in the original NDA. The three studies were similar in terms of clinical and radiographic criteria for enrollment and evaluation of outcome, but differed in other respects. Study 3011 was a randomized, double-blind, active control trial comparing 5 days of telithromycin with 10 days of cefuroxime axetil. Sinus puncture was performed at entry into this study for microbiological diagnosis. Study 3002 was a randomized and double-blind comparison of 5 days versus 10 days of telithromycin, but did not include a control drug. This study also included sinus puncture at baseline. Study 3005 was a randomized double-blind, active control trial comparing telithromycin for 5 days, telithromycin for 10 days, and amoxicillin/clavulanate for 10 days. Sinus puncture was not required for study entry. The daily dose of telithromycin (800 mg once daily) was the same in all telithromycin-treated patients, regardless of the duration of telithromycin treatment.

The clinical outcomes at the test-of cure visit for the three studies are shown in the table on the following page. The applicant seeks approval for a 5-day dose regimen of telithromycin for ABS, so the columns on the left show the results for the 5-day treatment course of telithromycin. The results of the 10-day treatment course from study 3005 are not shown, but were similar to the results for the 5-day regimen. No advantage was seen to giving 10 days of telithromycin compared to the 5-day regimen.

Clinical Outcomes at Test-of-Cure in ABS Studies

	Telithromycin 5-Days			Comparators 10-Days				2-sided 95% Confidence Interval
	N	Cure	%	Comparator	N	Cure	%	
PPc Population								
Study 3002 [1]	123	112	91.1	TEL 10-D	133	121	91.0	(-7.7%, 7.9%)
Study 3005	146	110	75.3	AMC	137	102	74.5	(-9.9%, 11.7%)
Study 3011	189	161	85.2	CXM	89	73	82.0	(-7.1%, 13.4%)
MITT Population								
Study 3002	167	138	82.6	TEL 10-D	168	147	87.5	(-13.1%, 3.3%)
Study 3005	201	140	69.7	AMC	202	138	68.3	(-8.2%, 10.9%)
Study 3011	240	193	80.4	CXM	116	84	72.4	(-2.2%, 18.2%)

[1]Study 3002 compared two dosing regimens of TELITHROMYCIN (5 days vs. 10 days).
TEL 10-D = telithromycin 10-Days, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil
Confidence interval is for the difference of the two cure rates.

The following tables provide the pathogen-specific cure rates for ABS patients treated with 5 days of telithromycin or control drug, from studies 3005 and 3011. Although study 3005 was not designed to collect microbiological samples from all patients, there were a few patients in whom microbiology data were reported. The results from study 3002, comparing 5 days to 10 days of telithromycin are not included in these tables. The results for patients treated with 10 days of telithromycin in study 3005 are not shown. The cure rates by pathogen appear similar for telithromycin-treated and comparator-treated patients.

Pathogen-Specific ABS cure rates in the MITT population

Organism	Telithromycin 5-d	Comparator
S. pneumoniae	82.5% (33/40)	81% (17/21)
H. influenzae	86% (37/43)	83.3% (15/18)
M. catarrhalis	100% (9/9)	87.5% (7/8)
S. aureus	90% (9/10)	66.7% (2/3)

Pathogen-Specific AECB cure rates in the PP population

Organism	Telithromycin 5-d	Comparator
S. pneumoniae	87.1% (27/31)	87.5% (14/16)
H. influenzae	82.4% (28/34)	86.7% (13/15)
M. catarrhalis	100% (7/7)	100% (7/7)
S. aureus	100% (8/8)	66.7% (2/3)

In study 3002, the clinical outcomes for patients treated with 5 days of telithromycin at the test-of-cure visit were comparable to the results in the above tables. In the MITT population treated with 5 days of telithromycin in study 3002, clinical outcomes were 29/37 (78.4%) patients with *S. pneumoniae*, 15/16 (93.8%) for patients with *H. influenzae*, 7/8 (87.5%) for patients with *M. catarrhalis*, and 5/6 (83.3%) for patients with *S. aureus*. For *S. aureus* to be considered the pathogen in these analyses, the organism

had to be isolated by sinus puncture, had to be present in at $\geq 10^4$ CFU and the predominant organism, and had to be the sole ABS pathogen identified.

Telithromycin (800 mg once daily for 5 days) can be approved for treatment of acute bacterial sinusitis based on clinical outcomes that were non-inferior to cefuroxime and amoxicillin/clavulanate. Pathogen specific clinical outcomes for ABS patients were acceptable.

Community-Acquired Pneumonia

The submission for community-acquired pneumonia (CAP) is the largest in terms of the number of studies performed, particularly because the applicant was seeking claims for activity against antibiotic-resistant strains of *Streptococcus pneumoniae*. It is also the most complex to summarize, because it involved submissions of new data or analyses to each of the three review cycles for this NDA.

In the original NDA, there were three controlled trials of CAP (studies 3001, 3006, and 3009) and three open label studies (studies 3000, 3009OL, and 3010). The results of these studies are shown in the table below. Telithromycin-treated CAP patients received 800 mg once daily for 7 to 10 days, depending on the duration specified in the protocol.

CAP Clinical Outcomes at Test-of-Cure in CAP Studies (Original NDA)

	Telithromycin				Comparators				2-sided 95% Confidence Interval
	Regimen	N	Cure	%	Regimen	N	Cure	%	
PPc Population*									
Study 3001	TEL 10 d	149	141	94.6	AMX 10 d	152	137	90.1	(-2.1%, 11.1%)
Study 3006	TEL 10 d	162	143	88.3	CLA 10 d	156	138	88.5	(-7.9%, 7.5%)
Study 3009	TEL 7-10 d	80	72	90.0	TVA 7-10 d	86	81	94.2	(-13.6%, 5.2%)
Study 3000**	TEL 7-10 d	197	183	92.9	-	-	-	-	
Study 3009OL**	TEL 7-10 d	187	175	93.6	-	-	-	-	
Study 3010**	TEL 7 d	357	332	93.0	-	-	-	-	
MITT Population*									
Study 3001	TEL 10 d	199	171	85.9	AMX 10 d	205	161	78.5	(-0.5%, 15.3%)
Study 3006	TEL 10 d	204	161	78.9	CLA 10 d	212	171	80.7	(-9.9%, 6.5%)
Study 3009	TEL 7-10 d	100	82	82.0	TVA 7-10 d	104	89	85.6	(-14.7%, 7.5%)
Study 3000**	TEL 7-10 d	240	191	79.6	-	-	-	-	
Study 3009OL**	TEL 7-10 d	212	182	85.8	-	-	-	-	
Study 3010**	TEL 7 d	418	357	85.4	-	-	-	-	

* *PPc = Clinical Per-protocol Population, MITT = Modified Intent-to-treat Population*

** *Studies which did not include an active control arm*

TEL = telithromycin, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin, Confidence intervals are for the difference of the two cure rates.

All trials enrolled patients with mild-to-moderate CAP who were considered appropriate for outpatient treatment with an oral antibiotic. These trials had similar enrollment criteria, study procedures, and outcome measures. The primary efficacy endpoints for the studies were clinical cure rates at the test-of cure visit. Of particular note, one of the controlled studies (3009) was converted to an open-label trial (3009OL) when the use of trovafloxacin was restricted to serious infections in hospitalized patients. This explains the lower numbers of enrolled patients and wider confidence intervals in study 3009. In studies 3001 and 3006, telithromycin demonstrated non-inferiority to the comparator drugs. At the time of FDA action on the original NDA submission, the indication of CAP was considered to be approvable, pending additional information on the safety of telithromycin. Additional data to support efficacy in the treatment of penicillin-resistant and/or macrolide-resistant strains of *Streptococcus pneumoniae* were also requested in the approvable letter sent to the applicant on June 1, 2001.

The NDA resubmission of July 24, 2002 included the results of two new studies of CAP, a comparative study (4003) and an open-label, non-comparative trial (3012). The table below shows the applicant's clinical outcome assessment for these trials. Study 4003 was designed as a three-arm trial, comparing 5 days or 7 days of telithromycin (800 mg once daily) with 10 days of clarithromycin. The 95% confidence interval for the primary comparison (7 days of telithromycin versus 10 days of clarithromycin) in the trial is shown. Study 3012 was an open label study of 7 days of telithromycin. The resubmission provided an interim analysis of study results for the open-label trial. Enrollment in this trial was ongoing. The trials had similar enrollment criteria, study procedures, and outcome measures compared to the studies in the original NDA. The results were consistent with the outcomes from studies in the original NDA.

CAP Clinical Outcomes at Test-of-Cure in CAP Studies (NDA Resubmission)

	Telithromycin				Comparators				2-sided 95% Confidence Interval
	Regimen	N	Cure	%	Regimen	N	Cure	%	
PPc Population*									
Study 4003	TEL 7 d	161	143	88.8	CLA 10 d	146	134	91.8	(-10.2%, 4.3%)
Study 4003	TEL 5 d	159	142	89.3	"	"	"	"	--
Study 3012**	TEL 7 d	473	424	89.6	-	-	-	-	--
MITT Population*									
Study 4003	TEL 7 d	157	191	82.2	CLA 10 d	181	147	81.2	(-7.4%, 9.4%)
Study 4003	TEL 5 d	187	154	82.4	"	"	"	"	--
Study 3012**	TEL 7 d	538	447	83.1	-	-	-	-	--

** PPc = Clinical Per-protocol Population, MITT = Modified Intent-to-treat Population*
*** Study which did not include an active control arm*
TEL = telithromycin, CLA= clarithromycin

Outcomes for patients from the controlled clinical studies are summarized by pathogen in the following tables. The tables include only the results for patients from controlled clinical trials. The results for evaluable patients identified with atypical pathogens are also shown. Overall, the cure rates by pathogen were similar for telithromycin-treated and comparator-treated patients.

Pathogen-Specific CAP Cure Rates in the MITT Population (Controlled Studies)

Organism	Telithromycin	Comparator
S. pneumoniae	82.6% (90/109)	76% (79/104)
H. influenzae	76.5% (65/85)	85.3% (64/75)
M. catarrhalis	78.9% (15/19)	64.3% (9/14)

Pathogen-Specific CAP Cure Rates in the PP Population (Controlled Studies)

Organism	Telithromycin	Comparator
S. pneumoniae	93.6% (73/78)	90% (63/70)
H. influenzae	83% (39/47)	95.5% (42/44)
M. catarrhalis	85.7% (12/14)	77.8% (7/9)
Chlamydophila pneumoniae	92.0% (23/25)	94.7% (18/19)
Mycoplasma pneumoniae	95.7% (22/23)	90.9% (20/22)

The additional studies (3012 and 4003) in the NDA resubmission were provided with an analysis of outcomes in patients with CAP due to penicillin-resistant and macrolide-resistant strains of *Streptococcus pneumoniae* (PRSP and MRSP, respectively). In the resubmission, the collected cases of CAP due to PRSP or MRSP were summarized. The outcomes for these CAP patients with antibiotic-resistant *S. pneumoniae* are described in the following paragraphs, as part of the data supporting a claim for treatment of CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP). At the time of the action on the resubmission, substantial evidence had been provided to support a claim of CAP due to PRSP, but additional safety information was still needed.

In the 3rd submission, the applicant provided analyses of the cases of CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP[1]) to support a labeling claim. The FDA had approved a labeling claim for CAP due to MDRSP for Factive® (gemifloxacin mesylate) Tablets. The applicant provided these analyses to support their own claim for MDRSP. A few additional cases of CAP due to MDRSP were reviewed as part of the 3rd submission, and summarized in an addendum to the efficacy review.

There were a total of 48 patients with MDRSP from the eight CAP clinical trials. One of these subjects was considered to have an indeterminate outcome by the applicant and FDA. This subject was excluded from the analyses of MDRSP, leaving 47 patients with CAP due to MDRSP in the MITT analysis. There were a total of 36 evaluable patients with CAP due to MDRSP. The clinical outcomes for patients with CAP due to MDRSP were 38/47 (80.1%) in the MITT population and 33/36 (91.7%). The following tables

[1] MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

show the clinical outcomes for telithromycin-treated patients with CAP due to antibiotic-resistant *S. pneumoniae*. Other than eight subjects with *S. pneumoniae* with resistance to erythromycin only, the other patients described in the table had MDRSP isolates. Since MDRSP, by definition, includes isolates with resistance to more than one of these antibiotics, individual patients are included in more than one row of each table. Clinical outcomes in CAP patients with MDRSP were similar overall to outcomes in CAP patients with *S. pneumoniae*.

Clinical Outcome for Patients with CAP due to Antibiotic-Resistant S. pneumoniae Treated with Telithromycin – MITT Population

Antimicrobial	Clinical Cure Rate	%
Penicillin[+]	23/31	74.2
Cefuroxime[+]	23/30	76.7
Erythromycin[*]	36/44	81.8
Tetracycline/doxycycline	15/20	75.0
TMP/SMX[+]	27/35	77.1

**: This includes 8 isolates that are resistant to erythromycin only, 7 were clinical cures.*
+: One patient was considered to have an indeterminate outcome and was excluded from these analyses.

Clinical Outcome for Patients with CAP due to Antibiotic-Resistant S. pneumoniae Treated with Telithromycin – PP Population

Antimicrobial	Clinical Cure Rate	%
Penicillin	20/23	86.9
Cefuroxime	20/22	90.9
Erythromycin[*]	32/36	88.9
Tetracycline/doxycycline	11/13	84.6
TMP/SMX	24/27	88.9

**: this includes 8 isolates that are resistant to erythromycin only, 7 were clinical cures*

Overall, the results of the controlled clinical studies and the pathogen specific cure rates provide substantial evidence to support the approval of telithromycin for the treatment of community-acquired pneumonia. The additional data in patients with antibiotic-resistant isolates support a claim for treatment of CAP patients with MDRSP.

Tonsillitis/Pharyngitis

Two studies of Tonsillitis/Pharyngitis (T/P) due to group A beta-hemolytic *Streptococcus pyogenes* were submitted in the original NDA for telithromycin. The studies were multicenter, double-blind, active controlled trials comparing oral telithromycin (800 mg once daily) for 5 days with 10 days of penicillin or clarithromycin. The primary efficacy endpoint of the clinical trials was comparison of bacteriological outcome between telithromycin and comparator in the per protocol population with group A beta-hemolytic Streptococci (GABHS) on baseline throat cultures. The following table shows the bacteriological outcomes in the PP and MITT populations in the T/P trials.

Bacteriological Outcomes at Test-of-Cure in T/P Studies

	Telithromycin 5-Days			Comparators 10-Days				2-sided 95% Confidence Interval
	N	Cure	%	Comparator	N	Cure	%	
PP Population								
Study 3004	115	97	84.3	PCN	119	106	89.1	(-14.3%, 4.8%)
Study 3008	150	137	91.3	CLA	135	119	88.1	(-4.6%, 11.0%)
MITT Population								
Study 3004	138	110	79.7	PCN	150	119	79.3	(-9.0%, 9.7%)
Study 3008	187	152	81.3	CLA	173	134	77.5	(-5.1%, 12.8%)

PP = Per-protocol Population, MITT = Modified Intent-to-treat Population
PCN = penicillin V potassium, CLA = clarithromycin,
Confidence interval is for the difference of the two cure rates.

Telithromycin did not demonstrate equivalence to penicillin in the bacteriological outcome in study 3004. Cure rates of <85% in study 3004 and in the MITT population for study 3008 would allow, at best, a claim for use as a second line agent.

The studies did include some information on patients with erythromycin-resistant strains of GABHS. The following table shows the bacteriological outcomes (eradication rates in subjects with erythromycin-resistant GABHS. Although the numbers of subjects were small, telithromycin appeared to be less effective than penicillin for treatment of erythromycin-resistant GABHS than penicillin.

Eradication Rates in Subjects with Erythromycin-Resistant GABHS

	Telithromycin 5-Days			Comparators 10-Days			
	N	Cure	%	Comparator	N	Cure	%
PP Population							
Study 3004	6	1	16.7	PCN	9	8	88.9
Study 3008	5	2	40	CLA	4	0	0

The adverse events profile of telithromycin was also a concern in the T/P studies. It was in the T/P studies where visual adverse effects of telithromycin were most notable. The T/P population includes younger patients, who appear to be at higher risk of developing visual adverse effects from telithromycin.

A non-approval letter for the T/P indication was issued on June 1, 2001 for several reasons. Telithromycin did not demonstrate equivalence to penicillin in study 3004. The eradication rates of <85% would not have allowed a claim as a first-line agent. Activity

did not appear to be retained against erythromycin-resistant GABHS. The adverse effects of telithromycin, particularly the visual AE noted in the T/P trials, did not support the use of telithromycin in the treatment of tonsillitis/pharyngitis.

Summary of Agency Conclusions and Action

Substantial evidence of efficacy for patients with community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis has been demonstrated. There was sufficient experience in patients with pneumonia due to multi-drug-resistant *Streptococcus pneumoniae* to grant this claim. The overall assessment of safety finds an acceptable risk-benefit profile for Ketek™ (telithromycin) Tablets for these indications.

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/s/

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Medical Team Leader Memorandum – NDA 21-144 (telithromycin)

I. Executive Summary

Streptococcus pneumoniae remains the most common bacterial cause of community-acquired pneumonia (CAP) in the U.S. Since macrolides are widely used for empiric therapy of CAP, the recent spread of *in vitro* resistance to this class of antimicrobials has raised concerns over possible treatment failures of this prevalent and potentially life-threatening infection. However, it is unclear whether this *in vitro* resistance is clinically significant.

Telithromycin is a new antimicrobial, chemically related to macrolides, but with *in vitro* activity against macrolide-resistant strains of *S. pneumoniae*. In February 2000, Aventis Pharmaceuticals submitted a NDA for this NME under the trade name of Ketek™, proposing its use in a variety of respiratory tract infections, including CAP due to penicillin- or macrolide-resistant *S. pneumoniae*. Review of the original NDA raised significant safety concerns, including:

- Potential telithromycin hepatotoxicity, based on toxicologic studies, a cluster of transaminase elevations in elderly telithromycin-treated patients, and a case of biopsy-confirmed eosinophilic hepatitis in a telithromycin-treated patient.
- Potential CYP 3A4-mediated drug interactions (including QT prolongation).
- Telithromycin-related visual blurring.
- Few data on patients with co-morbidities or receiving potentially interacting drugs.
- The implications of these factors in light of anticipated broad population exposure.

These issues were discussed at an April 2001 meeting of the Anti-Infective Drugs Advisory Committee. The Committee voted in favor of approval for CAP but against approval for CAP due to resistant pathogens, and recommended submission of additional safety data, studying use of telithromycin in patients with co-morbidities or receiving potentially interacting medications. The FDA subsequently issued an approvable letter for the NDA, requesting that the Applicant perform a large usual care safety study in examining the potential toxicities of telithromycin with regard to cardiac, hepatic, visual, and vascular safety; additional data regarding the efficacy of telithromycin in the treatment of CAP due to penicillin- or macrolide-resistant *S. pneumoniae*; and clinical pharmacology studies examining the pharmacokinetics and electrophysiologic effects of telithromycin in subjects with impaired clearance of this drug, as well as clinical pharmacology studies of the visual effects of telithromycin.

The Applicant submitted the requested studies in July 2002; these were discussed at a January 2003 AIDAC meeting, at which the Committee felt that safety and efficacy for the requested indications had been demonstrated, in large part on the basis of the large safety study and foreign post-marketing data. However, review of the amended NDA has identified the following outstanding issues:

- Serious concerns over data integrity in the large usual care safety study
- Incomplete reporting by the Applicant of foreign post-marketing safety data

The Applicant claims advantages for telithromycin over existing agents in the treatment of community-acquired pneumonia because of its activity against macrolide-resistant strains of *S. pneumoniae*. However, the magnitude of this benefit, if any, remains uncertain. It appears likely that there is little or no benefit to use of telithromycin in less serious indications such as acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis, because of the lack of evidence demonstrating clinical relevance of penicillin or macrolide resistance in these infections. Given this uncertainty as to the marginal benefit provided by telithromycin over existing agents, and because description of the risk profile of telithromycin and assessment of its risk-benefit ratio (particularly with regard to hepatic and visual toxicities) rest heavily on the large safety study and post-marketing data, resolution of these issues is critical; additional data is needed before a final regulatory decision on approval (including labeling issues) can be made.

II. Regulatory History

A. Original NDA

The original New Drug Application (NDA) for telithromycin (Ketek™) was submitted on February 28, 2000. The Applicant (Aventis Pharmaceuticals, Inc.) requested approval for marketing of telithromycin in the United States for the following indications in adults:

- tonsillopharyngitis;
- acute bacterial exacerbation of chronic bronchitis (ABECB);
- acute bacterial sinusitis (ABS);
- community-acquired pneumonia (CAP)

The Applicant submitted efficacy and safety data from 13 Phase 3 trials, comprising 3265 telithromycin-treated patients (2045 in comparative trials), and 1672 comparator-treated patients. The Applicant also submitted data on cases of CAP associated with erythromycin-resistant isolates of *S. pneumoniae* from a comparative study conducted in Japan.

In addition, the Applicant submitted data from 650 telithromycin-treated subjects in Phase 1 studies examining the drug's safety profile and clinical pharmacology, as well as from drug interaction studies enrolling 261 subjects who received multiple oral doses of 800 mg telithromycin. Subjects in these studies were healthy adults, generally less than 50 years old.

Finally, the Applicant submitted toxicologic, microbiologic, chemistry, and manufacturing data in support of the NDA.

A 4 month safety update was submitted on June 30, 2000, and a major clinical amendment was submitted on February 27, 2001.

B. April 2001 Anti-Infective Drugs Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee (AIDAC) met on April 26, 2001 to discuss safety and efficacy data for telithromycin. The Committee heard presentations by the Applicant, FDA, and cardiology and hepatology consultants. Safety discussions focused on telithromycin's effects on cardiac repolarization (increased QT interval), hepatic adverse events, and blurred vision, while efficacy centered on patients with CAP due to penicillin-resistant *Streptococcus pneumoniae* (PRSP) or macrolide-resistant *S. pneumoniae* (MRSP). The Committee voted against approval and recommended additional studies to delineate safety, particularly in "at risk" populations, and efficacy in patients with CAP due to drug-resistant *S. pneumoniae* and *Haemophilus influenzae*.

Efficacy analyses presented to the Committee by the Applicant and FDA were in general agreement with regard to pneumonia, sinusitis, and bronchitis. The Agency's presentation on tonsillopharyngitis concluded that regulatory criteria for efficacy in this infection had not been met and the Committee "tabled" discussion on this indication. In general, the Committee felt that the data did not support a claim for PRSP or MRSP, citing insufficient numbers of patients, few bacteremic patients, relatively low success rates in bacteremic patients, and some concern about the clinical significance of macrolide resistance in community-acquired pneumonia.

Discussion of telithromycin safety data and analyses focused primarily on cardiac repolarization, hepatotoxicity in animals and man, and complaints of blurred vision. There was general agreement that telithromycin has a modest concentration-dependent effect on cardiac repolarization. Concerns arose for "at risk" patients who may have greater exposure to the drug (e.g., elderly, patients with hepatic and/or renal impairment, etc.), together with one or more amplifying factors (e.g., concomitant medications that increase drug exposure via cytochrome P450 metabolic pathways, hypokalemia, congestive heart failure, etc.) The Committee considered the data in patients with multiple risk factors to be very limited and specifically recommended additional safety and pharmacokinetic studies in the elderly, patients with

hepatic and/or renal impairment, and those on multiple concomitant medications, to allow for analysis of drug-drug interactions.

Hepatic effects were noted in both preclinical and clinical studies. In animals, all species tested (dogs, rats, and monkeys) showed evidence of hepatotoxicity. In comparing the effects in animals given telithromycin versus clarithromycin, the FDA reviewer noted that the hepatotoxic effects of telithromycin were greater. In Phase 1 studies that included 8 elderly subjects administered a single 2.0 gram dose of telithromycin, 3 patients had elevated liver transaminase values (ALT and AST levels ranging from 100-300, ALT > AST). Phase 1 data showed no clear dose-response for hepatic adverse events. In Phase 3 studies, 2 patients experienced serious hepatic adverse events possibly associated with telithromycin. One patient underwent a liver biopsy, read by a FDA consultant from the Armed Forces Institute of Pathology (Zachary Goodman, M.D.) as consistent with drug-induced liver injury. A second biopsy nine months later was consistent with autoimmune hepatitis, possibly resulting from neoantigen exposure after drug injury.

Visual complaints were noted in telithromycin-treated patients in Phase 3 studies of pneumonia, sinusitis, and pharyngitis. Blurred vision possibly related to study drug occurred in 11 (0.3%) telithromycin-treated patients and 0 comparator-treated patients. Patients were typically < 40 years of age and female. Duration of blurred vision ranged from hours to 10 days.

Given the risks of cardiac and hepatic toxicity of telithromycin, the Committee felt that the efficacy data supported the use of telithromycin in CAP, but not in other respiratory tract infections; furthermore, the Committee felt that the data were insufficient to support a claim for CAP due to PRSP or ERSP.

With regard to the efficacy of telithromycin in treating CAP due to resistant strains of *S. pneumoniae,* members of the Committee expressed a need for more studies and more patient information, particularly in treating bacteremic patients and also resistant organisms. They felt that the numbers of patients were small, particularly for patients with bacteremic pneumonia. They indicated a need for more data on cross-resistance between macrolides and telithromycin, and expressed concern over possible emergence of telithromycin-resistant pneumococci during therapy.

With regard to the safety profile of telithromycin, the Committee was concerned over the lack of safety data from patients receiving concomitant medications (particularly 3A4 inhibitors) or patients with co-morbid conditions such as renal insufficiency. The Committee indicated that more data on safety from pre-marketing studies of older patients were needed to define drug interactions. The Committee also expressed concern over the potential for hepatotoxicity associated with telithromycin. The Committee recommended a large safety study to better describe drug risks, particularly the potential for hepatotoxicity. Additional pre-marketing studies were considered preferable to post-marketing surveillance alone to assess safety.

In summary, the Committee recommended establishing a more complete toxicity risk profile in larger numbers of patients likely to receive telithromycin, and submission of more efficacy data on the use of telithromycin in CAP due to resistant organisms.

C. Regulatory Action (June 1, 2001)

After considering the results of the FDA review of this NDA and the recommendations made by the AIDAC, the FDA issued an approvable letter on June 1, 2001 for the indications of AECB, ABS, and CAP. The letter requested that the Applicant perform a large safety study to gather data on cardiac, hepatic, visual, and vasculitic adverse events in a patient population representative of that likely to be seen in usual clinical practice. Additional data was requested on the efficacy of telithromycin in the treatment of infections due to PRSP and ERSP. In addition, the Applicant was asked to characterize drug exposure and cardiac repolarization effects in patients at risk for multiple perturbations of drug elimination pathways and conduct Phase 1 studies of the visual effects of telithromycin.

A nonapprovable letter was issued for the indication of tonsillopharyngitis.

D. NDA Amendment

In response to the approvable letter, the Applicant submitted an amendment to the NDA for telithromycin on July 24, 2002, containing the following new studies and data:

Safety

Study 3014 – A randomized, open-label multi-center trial of the safety and effectiveness of telithromycin versus amoxicillin-clavulanic acid in outpatients with respiratory tract infections in usual care setting. This study was intended to address the request for a large safety study to examine adverse events of special interest (cardiac, hepatic, visual, and vasculitic).

The applicant also submitted a Periodic Safety Update Report covering the period July 9, 2001 to January 9, 2002, and a line listing of adverse events reported between January 9, 2002 and April 24, 2002.

Efficacy in PRSP and ERSP infections

Three new CAP studies (two comparative, one uncontrolled) were submitted. These studies were intended to address the request for additional data on the efficacy of telithromycin in the treatment of infections due to PRSP and ERSP. The Applicant also submitted data from a new study of telithromycin in the treatment of ABECB.

Clinical Pharmacology

The Applicant submitted data from a pharmacokinetic study of telithromycin co-administered with a potent cytochrome P450 3A4 (CYP3A4) inhibitor in elderly subjects with diminished renal function. The study included assessment of QT interval changes. A second study assessed multiple-dose telithromycin pharmacokinetics in renally impaired patients. This study also included assessment of QT interval changes. These studies were intended to address the request to characterize drug exposure and cardiac repolarization effects in patients at risk for multiple perturbations of drug elimination pathways. In addition, the Applicant studied multiple-dose telithromycin pharmacokinetics in hepatically impaired patients.

The applicant also conducted Phase 1 studies of the visual effects of supratherapeutic doses of telithromycin in healthy young and older subjects. Extensive ophthalmologic evaluations were performed, along with measurements of telithromycin concentrations in plasma and tears.

E. January 2003 Anti-Infective Advisory Committee Meeting

At the January 2003 AIDAC meeting, the Committee heard presentations from the Applicant, FDA, and consultants regarding the new data submitted. The discussion centered on the strength of the evidence for efficacy in CAP due to resistant organisms, hepatic toxicity, and visual adverse events. The Committee concluded that efficacy in CAP due to PRSP and MRSP had been demonstrated; however, there was relatively little discussion of the public health impact of macrolide resistance in *S. pneumoniae*.

The discussion of hepatic toxicity centered on the findings from Study 3014, the post-marketing data and the case of telithromycin-associated eosinophilic hepatitis mentioned in section IIB. Because of incomplete reporting of post-marketing data (as noted below), the Applicant's discussion of these data included details not available to FDA reviewers. The Committee heard presentations from an FDA pathology consultant from the National Institutes of Health (David Kleiner. M.D., Ph.D.) who agreed with the AFIP assessment that this case represented drug-related hepatic injury; a second FDA consultant (William Lee, M.D.) also agreed with this assessment. In contrast, a consultant retained by the Applicant attributed the presence of eosinophils in the liver biopsy to a concurrent asthma attack. Dr. Lee stated that telithromycin is clearly hepatotoxic, but the data presented suggest that it is not significantly more hepatotoxic than marketed macrolides; he also indicated that differences in toxicity between telithromycin and macrolides may only become evident during post-marketing surveillance.

The discussion of visual adverse events centered on the mechanism and implications of visual blurring associated with telithromycin. In Phase 1 studies, in patients receiving supratherapeutic doses of telithromycin, the duration of blurring was 2.8 h (range 0.8 – 20.3 h); the incidence was higher in younger

patients, who also showed higher telithromycin concentrations in tears. These studies also suggest that telithromycin-associated visual blurring is related to delays in accommodation and release of accommodation. The data from Phase 3 studies suggested that the incidence of this event is about 0.6%, with a mean duration of 3.3 d (range 0 – 10 d). Interestingly, the incidence of blurring in Phase 3 studies was higher in patients receiving a 3A4 inhibitor. Given that this drug is intended for use primarily in the outpatient setting, the Committee expressed reservations about patients receiving telithromycin driving or engaging in other activities requiring visual acuity.

The Committee voted to recommend approval of telithromycin for CAP (including cases due to PRSP and MRSP), as well as the other indications requested. However, The Committee also indicated that the drug should be labeled appropriately regarding the risk of hepatic injury and visual adverse events.

III. Outstanding Regulatory Issues

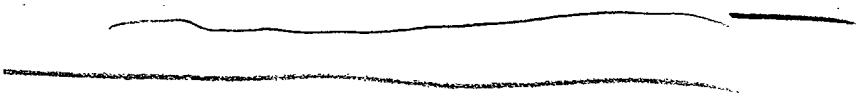
A. Data integrity issues

Confidence in the reliability and integrity of data from Study 3014 is essential, given the central role of this study in assessing the safety profile of telithromycin. However, all sites inspected thus far have revealed problems raising concerns over data integrity. The review division asked the Division of Scientific Investigations (DSI) conduct inspections of appropriate sites for study 3014. The Applicant recruited investigators at 1,872 sites to conduct this study. Given this large number of sites and the resources available to DSI, a decision was made to initially inspect only the highest enrolling site (Dr. Anne Kirkman-Campbell). The inspection revealed a number of serious GCP violations, particul[illegible]

- Enrollment of patients who were being seen for weight loss therapy, rather than the conditions specified in the protocol.
- Documentation of patients as having completed courses of therapy despite statements from patients that they had not received medication.
- Enrollment of patients in numbers far in excess of those approved by the local IRB, without IRB review
- Enrollment of patients documented as being ineligible for the study on the basis of drug allergies.

Other concerning findings included:

- Enrollment of members of the investigator's family
- Enrollment of members of the investigator's staff
- Absence of any reported adverse events for the first 100 patients; according to DSI, after being confronted by the contract research organization (CRO) monitoring the site, the investigator began reporting adverse events for subsequent patients



The Applicant did not alert the Agency to any problems with this site. However, at a face-to-face meeting on December 19, 2002, the Applicant indicated that they had been aware of problems at this site. No explanation was given for the decision to retain this investigator in the study or to not communicate the problems found by the Applicant with this investigator to the review division.

Because of the results of this inspection, DSI was asked to inspect the next two highest enrolling sites. These inspections revealed significant irregularities at the second-highest enroller (enrollment of ineligible patients, incomplete laboratory testing, failure to use drug accountability logs). The

investigator at the third-highest enrolling site (Dr. [redacted] was found to have been on probation at the time of the study (for gross medical negligence and failure to keep adequate medical records). Seven weeks after seeing his last patient in this study, this investigator was arrested on drug, weapons, and assault charges; his medical license was suspended. The inspection of this investigator's site was significant for use of white-out in study records. The Applicant claimed to be unaware of the series of events involving Dr. [redacted] or any problems at these sites.

The settings in which high enrollment occurred also raised concern over data integrity. Of the top 30 enrollers, 8 enrolled 1% or more of the adult population of the cities in which they were located. Although in a few sites high enrollment may be explained by proximity to large urban areas, for others the actual enrollment is inconsistent with the enrollment predicted on the basis of the catchment population. Given the incidences of the respiratory tract infections under study and the investigational nature of this drug, this finding raises further concerns over data integrity in this study.

None of these issues regarding data integrity were presented at the January 2003 AIDAC meeting.

It is not clear to what extent these findings represent systematic problems with Study 3014. Given this, it is difficult to assess the study's scientific validity and the role of data from this study in assessing the risk profile of telithromycin. For these reasons, review of monitoring and audit data for Study 3014 is essential to determine whether this study can form a reliable component of the safety database for telithromycin for regulatory decision-making.

B. Post-marketing data

Foreign post-marketing reports represent another critical component of the safety database, since rare events such as drug-induced hepatic failure may become apparent only after a large number of exposures. Telithromycin was approved for marketing in the European Union in July 2001, and has been launched in Europe, Central America, and South America. The Applicant has stated that the post-marketing safety database includes [redacted] exposures, and that no cases of drug-related hepatic failure have been identified. The AIDAC relied on this component of the safety database in their recommendation to approve telithromycin.

However, post-marketing data provided to the FDA have been incomplete or reported in a dilatory fashion. It is not clear from the data provided by the Applicant that either quantitative or qualitative descriptions of post-marketing adverse events represent all data in the possession of the company. For example, despite extensive prescribing of telithromycin in Italy ([redacted] treatment courses), post-marketing adverse events were reported in only 25 patients.. When compared to the number of German patients reported as having post-marketing adverse events (218), the Italian rate is much lower. Submitted narratives of adverse events represent excerpts from the original reports edited by the Applicant; in at least one case involving possible hepatic injury, significant details were omitted from the excerpt submitted by the company. In another instance, post-marketing cases of telithromycin-treated patients undergoing liver biopsy to assess possible hepatic injury that were known to the Applicant 7 weeks (two patients) and five months (one patient) prior to NDA submission were not reported to the review division until five months into the six month review cycle, and then only after an explicit query from the division. The Applicant had previously stated that it did not know of any such cases.

Given these gaps in the submitted post-marketing data, complete information on foreign post-marketing events is required for review before any final decision on approval can be made.

The issues involving Study 3014 data integrity and completeness of the post-marketing database currently prevent a complete safety assessment of telithromycin, particularly for the hepatic and visual toxicity issues discussed below in IIIC and IIID. This in turn complicates decisions on final regulatory actions, including labeling if the NDA should be approved.

C. Visual risk profile

The visual risk profile of telithromycin is notable for the following:

- In placebo-controlled Phase 1 studies, in younger patients receiving a single 2400 mg dose of telithromycin, the incidence of blurred vision ranged from 26.7% to 83.3%. In older patients receiving this dose, the incidence of blurred vision ranged from 0% to 33%. Blurry vision developed 1 to 3 hours after dosing. In subjects developing blurry vision, the adverse event lasted up to 20 hours. One placebo-treated subject developed blurry vision. The effect was described as a difficulty to focus at far distance without any change in intraocular pressure or anterior chamber angle, without modification of the visual field or color vision or fundus. Blurred vision was associated in one case with a reduced near visual acuity and in 2 cases with a reduced amplitude of accommodation but not associated with alteration of far visual acuity, refraction or tear film. Detailed ophthalmologic examinations during the occurrence of blurry vision did not reveal any significant change from baseline.
- The mechanism of telithromycin-induced visual blurring appears related to delay in accommodation. However, older patients, who have decreased accommodative ability and who should therefore be less affected by telithromycin, also show visual blurring; the reason for this is not known.
- The concentration of telithromycin in tears was higher in younger subjects than in older subjects. At the 2400 mg dose at which the adverse event of blurred vision was elicited, the concentration of telithromycin in tear fluid was 341 ng/Schirmer strip in subjects aged 18-40 years, versus 201 ng/strip in subjects aged 50 to 65 years.
- In Phase 3 studies, the incidence of visual adverse events in telithromycin-treated patients in all controlled phase 3 studies (not including 3014) was 26/2702 (1.0%) and was 4/2139 (0.2%) among comparator-treated patients. Women were more likely to have visual adverse events during telithromycin treatment than were men (1.4% vs 0.5%). Of telithromycin-treated patients developing blurred vision, 16/20 (80%) were 40 or younger. The mean duration of blurry vision in these studies was 3.3 days (range, 1 – 10 days).
- In telithromycin-treated patients receiving a concomitant CYP 3A4 inhibitor in Phase 3 trials, the incidence of blurry vision was almost 5 times that in patients not receiving a 3A4 inhibitor (1.9% vs. 0.4%)
- In Study 3014, 74 (0.6%) of telithromycin-treated patients had a confirmed visual endpoint, versus 0.04% of comparator-treated patients. 33% of telithromycin-treated patients developing blurry vision reported a significant impact on activities; of the 17 subjects where a specific comment was included, 7 had difficulty reading, 5 were unable to work and one of these was also unable to drive, a further 4 were also unable to drive, and one was unable to baby-sit a grandson.
- As of the date of the writing of the January 2003 AC briefing document, post-marketing safety reports received by the FDA regarding telithromycin-treated patients in countries where telithromycin has been approved included 167 visual adverse events; 42 of these were considered serious.
- The current European Summary of Product Characteristics does not specifically mention visual adverse events. T

- No other antibacterial agent regulated by the FDA, including those intended for outpatient use, is known to cause this adverse reaction. In addition, the deputy director of the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products (Dr. Wiley Chambers) has indicated that he is unaware of any other drug product with such an abrupt onset of effect on accommodation.

D. Hepatic risk profile

The hepatic risk profile of telithromycin is notable for the following:

- Toxicologic studies show the liver to be the main site of telithromycin toxicity; the toxicology review of this NDA has shown that telithromycin is more hepatotoxic than macrolides.
- Telithromycin is metabolized by the 3A4 isoform of cytochrome P450, a potential pathway for generation of hepatotoxic metabolites
- In Phase 1 studies, a cluster of elderly subjects receiving a single 2 g dose of telithromycin showed elevations in serum transaminases.
- In the original NDA, a serious hepatic adverse event occurred in a telithromycin-treated patient with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration, changes strongly suggestive of a hypersensitivity type drug-related liver injury and similar to those described in cases of trovafloxacin-associated hepatitis. Several months later this patient went on to have an episode of asymptomatic elevations in his ALT and AST and a second liver biopsy showing changes consistent with chronic hepatitis, probably autoimmune, a finding consistent with neoantigen exposure after drug-related injury.
- The observed rate of possibly drug-related serious hepatic adverse events in Phase 3 trials was 2/4472 (0.0004%, 95% CI (0.0001. 0.0017). Of note, the mortality rate in cases of drug-induced hepatocellular injury may be as high as 10-15%; in addition, the number of prescriptions written annually in the U.S. for respiratory tract infections is greater than 80,000,000 (McCaig LF and Hughes JM. JAMA 1995; **273**:214-9).
- Analyses of liver function tests from the comparative Phase 3 studies in patients who were normal at baseline show a greater proportion of patients with low to moderate elevations (1-2x ULN, 2-3x ULN, and 3-5x ULN) of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the telithromycin-treated patients from the CAP studies. The AST and ALT elevations from patients in the CAP studies were present during the On-Therapy and Post-Therapy visits. Patients with concomitant transaminase and total bilirubin elevations were infrequent, but only found in telithromycin-treated patients and were categorized as low level elevations between 1x and 2x the upper limit of normal (ULN).
- Study 3014, the large safety study, compared telithromycin to amoxicillin/clavulanic acid; the latter agent is a recognized cause of cholestatic hepatitis.
- In Study 3014, there were five patients (three telithromycin and two amoxicillin-clavulanic acid) with hepatic endpoints (hepatic adverse events possibly related to study drug) adjudicated by the study's Clinical Evaluation Committee (CEC). The FDA medical reviewer agreed with the CEC's assessment of these cases. One telithromycin-treated patient in this group had a liver biopsy performed which showed cholestasis and "rare red dead hepatocytes"; however, the biopsy was performed more than three weeks after telithromycin treatment had ended. The FDA's pathology consultant assessed this biopsy as showing possible evidence of drug injury. The FDA medical reviewer assessed one other telithromycin-treated patient as having a possibly drug-related hepatic adverse events.
- Analyses of liver function tests in Study 3014 showed a higher rate of high (>8x ULN) transaminase elevations in telithromycin-treated patients compared to amoxicillin/clavulanic acid-treated patients. In addition, there was a higher incidence of such elevations in patients receiving 7 to 10 days of telithromycin compared to patients receiving 5 days of telithromycin.
- As of the date of the writing of the January 2003 AC briefing document, post-marketing safety reports received by the FDA regarding telithromycin-treated patients in countries where telithromycin has been approved included 54 hepatic adverse events; 19 of these were considered serious.

E. Cardiac risk profile

This issue is mentioned for sake of completeness; although full assessment of cardiac risk associated with use of telithromycin will require resolution of the issues surrounding Study 3014 and the post-marketing data, to date, there does not appear to be a signal that telithromycin is associated with a significant risk of serious ventricular dysrhythmias such torsades de pointes.

F. Drug-drug interactions

Telithromycin is a substrate for the CYP3A4 system and may have profound effects on the pharmacokinetics of other drugs interacting with this system. In particular, telithromycin has been shown to increase serum concentrations of simvastatin 700% when the two drugs are administered concomitantly. Because of the potential increase in toxicity risks associated with pharmacokinetic changes of this magnitude, it is important to fully characterize such interactions. The Applicant has reported completing multiple studies examining the interaction between telithromycin and simvastatin. However, as of the date of the January 2003 Advisory Committee meeting, data from these studies had not been submitted to the Agency for review.

IV. Regulatory Conclusions

A large number of outstanding regulatory deficiencies prevent a recommendation of approval for this amended NDA. These include:

- Uncertainty about the reliability of safety data from Study 3014.
- Lack of complete post-marketing information.
- Lack of important efficacy information, particularly data to support the clinical relevance of macrolide resistance in community-acquired pneumonia and of penicillin resistance in ABS and ABECB. In addition, efficacy information regarding lower response rates in patients infected with *Haemophilus influenzae* who are treated with telithromycin remain unexplained by the Applicant and is not reflected in the proposed labeling.
- Incomplete characterization of the visual risk profile of telithromycin.
- Incomplete pharmacokinetic information about drug interactions between telithromycin and simvastatin.

These holes in the data underlying risk-benefit calculations regarding telithromycin are magnified by the data suggesting that telithromycin may cause idiosyncratic hepatic reactions in combination with the potential population exposure associated with a drug used for common respiratory tract infections.

If data resolving these deficiencies were submitted to the agency, approval could be granted for the indication of community-acquired pneumonia, including cases due to penicillin-resistant *Streptococcus pneumoniae*. Approval for cases due to macrolide-resistant strains of *S. pneumoniae* could be granted if the Applicant submitted data and analyses supporting the clinical relevance of such strains. Such approval would be contingent on revision of the proposed labeling to accurately reflect the safety and efficacy of telithromycin and provide adequate directions for use, particularly with regard to visual adverse events. Approval for the indications of ABS or ABECB would depend on the final definition of the risk-benefit calculus and resolution of the issues regarding Study 3014 and post-marketing data.

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG SAFETY

PID# D040010

DATE: March 30, 2004

FROM: Ronald Wassel, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

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

SUBJECT: Consult:
Provide background data on the magnitude of visual adverse events and myasthenia gravis–type reactions seen with select antibiotics, for comparison with those events seen with telithromycin (Ketek™) from worldwide experience.

INTRODUCTION

Note: As telithromycin is not marketed in this country, there are few AERS cases (only two as a primary suspect drug) and they are not relevant to the issues addressed in this consult.

Telithromycin (Ketek™, NDA# 21-144) is the first of a new class of antimicrobials called ketolides that is currently under review for oral treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community–acquired pneumonia. It is chemically related to the macrolide antibiotic clarithromycin.

Visual adverse events, most often blurred vision, have represented the most commonly reported post-marketing events for telithromycin since approval in Europe and South America (July 2001). As stated in the Medical Officer's review, these events comprised approximately one-third of all patients with a reported post-marketing adverse event. Although the pathophysiology of the visual adverse events is poorly understood, data from Phase 1 studies, Phase 3 studies, and post-marketing adverse event reports (foreign database) are consistent with a disorder of accommodation as the primary disturbance. There have also been several post-marketing reports of severe myasthenia gravis associated with telithromycin exposure. In order to assess the sponsor's claim that telithromycin is similar to other approved antibiotics in its propensity to cause these events, a request was received from the Medical Officer reviewing the NDA safety data for a compilation of AERS data concerning these events reported with other selected antibiotics.

Specifically, the request included the following:

- Examine AERS data for visual adverse events associated with oral antibiotics that are commonly used to treat respiratory tract infections. In consultation with the Medical Officer, the list of antibiotics included macrolides (azithromycin, clarithromycin), quinolones (gatifloxacin, levofloxacin, and moxifloxacin), doxycycline, amoxicillin, and amoxicillin/clavulanate potassium. In addition, ethambutol and voriconazole were included for comparison because they are well-known to cause visual adverse events.

- Examine AERS data for reports of myasthenia gravis associated with macrolide antibiotics and include for comparison aminoglycosides and quinolones. In consultation with the Medical Officer, the list of antibiotics included azithromycin, clarithromycin, erythromycin, gentamicin, tobramycin, ciprofloxacin, and levofloxacin.

- Examine AERS data for reports of respiratory insufficiency and myasthenia in patients taking riluzole (Rilutek®, indicated for the treatment of patients with amyotrophic lateral sclerosis [ALS]) to determine if there is an additive effect from telithromycin since there was one death in a patient with ALS taking riluzole who developed respiratory insufficiency after taking telithromycin.

SEARCH TYPE AND DATE

AERS was searched on 1/22/2004.

SEARCH CRITERIA

Visual Adverse Events

Drugs: Amoxicillin, amoxicillin/clavulanate potassium, doxycycline, azithromycin, clarithromycin, gatifloxacin, levofloxacin, moxifloxacin, ethambutol, voriconazole (limited to oral route of administration)

MedDRA terms: Vision Disorders (HLGT)
Neurologic Visual Problems NEC (HLT)

Note: These MedDRA terms were chosen to capture a wide array of visual adverse events as different preferred terms may be used to report visual adverse events which are a part of the same adverse event syndrome. It is very common for different patients to report similar visual symptoms in different ways. However, the limitation in searching over a wide group of visual adverse events is that it does not account for related pathology among the different events.

The HLGT Vision Disorders is one of the highest level group terms within the Eye Disorders SOC. This group contains the HLTs related to amblyopia, blindness, color blindness, partial vision loss (under which the PT Vision blurred appears), refractive and accommodative disorders, visual color distortion, visual disorders NEC (which includes such terms as

diplopia, halo vision, optic nerve disorder, and visual disturbance), visual field disorders, and visual pathway disorders. Many of the same PTs are also included in the HLT Neurologic Visual Problems NEC, which added several additional PTs such as extraocular muscle paresis, optic ischemic neuropathy, optic neuritis retrobulbar, optic pathway injury, and strabismus.

Myasthenia gravis

Drugs: Azithromycin, clarithromycin, erythromycin, gentamicin, tobramycin, ciprofloxacin, levofloxacin (all routes of administration)

MedDRA terms: Neuromuscular Junction Dysfunction (HLT)

Note: The HLT Neuromuscular Junction Dysfunction contains the PTs Eaton-Lambert syndrome, myasthenia gravis, myasthenia gravis neonatal, myasthenic syndrome, neuromuscular blockade, and ocular myasthenia. Searching by this criteria would not retrieve potential cases of myasthenia gravis in which the event reports only described symptomatology (such as ptosis or muscle/limb weakness not defined as myasthenia) without a diagnosis of myasthenia gravis.

Riluzole

Drug: Riluzole

MedDRA terms: Respiratory Failures (Excl Neonatal) (HLT)
Neuromuscular Junction Dysfunction (HLT)

SEARCH RESULTS

A voluntary, spontaneous reporting system such as AERS only captures a fraction of all drug–related events that occur. It should be noted, the data in AERS cannot solely be used to reliably compare the relative risk of an adverse event among different drugs. These results include searches that involved a wide group of adverse events over varying time periods involving different patient populations obtained from different reporting sources.

Visual Adverse Events

Table 1 presents the data for the visual adverse event reports retrieved from AERS. The numbers are raw counts, which include duplicates and cases that otherwise might be excluded because of confounding factors. Also, the numbers reflect cases reported with the oral formulations of the drugs only. To provide some perspective, these numbers are presented in relation to the total number of reports in AERS for each of the drugs and to the total number of visual adverse event reports in AERS (using the MedDRA search criteria above).

Tables 2 through 6 provide a breakdown of the types of visual adverse events seen with each of the drugs. These data represent the number of cases after a review of the reports to remove

duplicates and exclude those that were considered not related to the drug in question. Typically, excluded cases were those judged to have been caused by other concomitant drugs, related to other medical reasons, to have a poor temporal relationship, or to have a negative dechallenge or rechallenge. Also, basic demographic data such as age, gender, and the source of the reports are included.

Table 1. Visual Adverse Event Data from AERS (raw counts as of 1/22/2004)

Total number of reports in AERS (all drugs, all AEs) – approximately 3 million

Search results using MedDRA terms *Vision Disorders (HLGT)* and *Neurologic Visual Problems NEC (HLT)*

Total number of reports (all drugs) – 30,827 (approx. 1% of total above)

Note: the following numbers are raw counts, which include duplicates and cases that otherwise might be excluded because of confounding factors. Also, the numbers reflect cases reported with the oral formulations of the drugs only.

	Total # visual AE reports (A)	Total # reports in AERS (all AEs) (B)	% of drug total that are VD/NVP reports (A) ÷ (B)
Doxycycline	56	1,901	2.9%
Amoxicillin/Augmentin	66	8,958	0.7%
Azithromycin/Clarithromycin	260	17,512	1.5%
Levofloxacin/Moxifloxacin/Gatifloxacin	194	7,091	2.7%
Ethambutol/Voriconazole	181	968	18.7%

Azithromycin and clarithromycin are grouped to represent the macrolide sample; levofloxacin, moxifloxacin and gatifloxacin are grouped to represent the fluoroquinolone sample; and ethambutol and voriconazole are grouped to represent the positive control sample of drugs known to cause visual adverse events.

Table 2. Doxycycline Vision Disorders

Total unduplicated cases	47
Excluded	15
Remaining	32

Reactions:

- Blurred vision 13
- Diplopia 10
- Visual field defect 3
- Visual disturbance 2
- Loss of vision 2
- Impaired color perception 1
- Optic neuritis 1

Demographics:

- Age (N=29): Range–12 to 86 yrs.; Mean–37.6 yrs.; Median–35 yrs.
- Sex (N=31): Male–15; Female–16
- Report source: Domestic–18; Foreign–14 (United Kingdom–8; Sweden–3)

Table 3. Amoxicillin/Augmentin Vision Disorders

Total unduplicated cases	58
Excluded	40
Remaining	18

Reactions:

- Blurred vision 12
- Vision abnormality 4
- Diplopia 2

Demographics:

- Age (N=12): Range–9 to 82 yrs.; Mean–37.1 yrs.; Median–38.5 yrs.
- Sex (N=17): Male–5; Female–12
- Report source (N=17): Domestic–16; Foreign–1

Table 4. Azithromycin/Clarithromycin Vision Disorders

Total unduplicated cases	233	
Excluded	142	
Remaining	91	Azithromycin–33; Clarithromycin–58

Reactions:

- Blurred vision 39
- Visual disturbance/abnormal vision 38
- Diplopia 11
- Impaired color vision 2
- Loss of vision 1

Demographics:

- Age (N=83): Range–18 months to 90 yrs.; Mean–51.5 yrs.; Median–53 yrs.
- Sex (N=89): Male–29; Female–60
- Report source: Domestic–78; Foreign–13

Table 5. Quinolone Vision Disorders

Total unduplicated cases	179	
Excluded	50	
Remaining	129	Moxifloxacin–52; Levofloxacin–50; Gatifloxacin–27

Reactions:

- Visual disturbance 72
- Blurred vision 35
- Loss of vision 9
- Diplopia 6
- Optic neuritis 5
- Papilledema 1
- Iritis 1

Demographics:

- Age (N=110): Range–17 to 86 yrs.; Mean–53.2 yrs.; Median–52.5 yrs.
- Sex (N=126): Male–40; Female–86
- Report source (N=126): Domestic–80; Foreign–46 (Germany–15)

Table 6. Ethambutol/Voriconazole Vision Disorders

Total unduplicated cases	176	
Excluded	31	
Remaining	145	Ethambutol–131; Voriconazole–14

Reactions:

- Visual disturbance 44
- Decreased acuity 31
- Optic nerve disorder/neuritis 28
- Loss of vision 19
- Blurred vision 15
- Blindness 7
- Diplopia 1

Demographics:

- Age (N=117): Range–13 to 89 yrs.; Mean–59.1 yrs.; Median–62 yrs.
- Sex (N=115): Male–63; Female–72
- Report source (N=143): Domestic–112; Foreign–31 (Japan–9; France–6)

Myasthenia gravis

Table 7 presents the data for neuromuscular junction dysfunction reports retrieved from AERS. The numbers are raw counts, which include duplicates and cases that otherwise might be excluded because of confounding factors. To provide some perspective, these numbers are presented in relation to the total number of reports in AERS for each of the drugs and to the total number of neuromuscular junction dysfunction reports in AERS (using the MedDRA search criteria above).

Tables 8 through 10 list those cases remaining following a review of the reports to remove duplicates and exclude those that were not truly myasthenia gravis–type reactions or were judged not related to the drug in question. Also, basic demographic data such as age, gender, and the source of the reports are included.

Table 7. Overall Neuromuscular Junction Dysfunction Event Data from AERS (raw counts as of 1/22/2004)

Total number of reports in AERS (all drugs, all AEs) – approximately 3 million

Search results using MedDRA term *Neuromuscular Junction Dysfunction (HLT)* (NJD)
This heading contains the preferred terms *Myasthenia gravis, Myasthenic syndrome,* and *Neuromuscular blockade,* among others.

Total number of reports (all drugs) – 1,375 (approx. 0.05% of total above)

Note: the following numbers are raw counts, which include duplicates and cases that otherwise might be excluded because of confounding factors.

	Total # NJD reports (A)	Total # reports in AERS (all AEs) (B)	% of drug total that are NJD reports (A) ÷ (B)
Azithromycin/Clarithromycin/Erythromycin	35	30,288	0.12%
Gentamicin/Tobramycin	5	7,500	0.067%
Ciprofloxacin/Levofloxacin	29	14,735	0.2%

Azithromycin, clarithromycin and erythromycin are grouped to represent the macrolide sample; gentamicin and tobramycin are grouped to represent the aminoglycoside sample; and ciprofloxacin and levofloxacin are grouped to represent the fluoroquinolone sample.

Table 8. AMINOGLYCOSIDES NEUROMUSCULAR JUNCTION DYSFUNCTION (N=4)

Hx	Age	Sex	Source	Drug	Onset	Sx	Outcomes
–	–	F	D	Gentamicin	–	Facial weakness	Unknown
N	18	F	D	Gentamicin	3 days	Numbness, stiffness, feeling of paralysis	Occurred during infusion, resolved after stopping
N	70	M	D	TOBI (inh)	1 week	Leg weakness (? due to bed-ridden)	Worsened after drug dc'd
N	93	F	D	Gentamicin	2 doses	Neuromuscular blockade	Hospitalization prolonged

Hx = history of myasthenia gravis
Source: D = domestic
Sx = symptoms experienced

Table 9. QUINOLONES NEUROMUSCULAR JUNCTION DYSFUNCTION (N=21)

Hx	Age	Sex	Source	Drug	Onset	Sx	Outcomes
–	–	–	F	Cipro	2 wks post tx	Diagnosed with MG	Unknown
Y	–	M	D	Levo	–	Exacerbation	Hospitalized
Y	–	–	D	Levo	–	Exacerbation	Unknown
N	–	M	D	Cipro	1 day	Arm weakness	Unknown
Y	26	F	D	Levo	1 day	Exacerbation	Intubation, plasmaphoresis
N	36	M	D	Cipro	Post tx	Muscle weakness, difficulty swallowing	No improvement
N	36	F	F	Nor/Cipro	During tx	Movement disorder, muscle weakness	Hospitalized
Y	36	F	F	Levo	1 day	Generalized asthenia, dyspnea	Hospitalized
N	37	M	D	Cipro	–	Leg weakness	Unknown
N	38	F	F	Cipro	–	Fatigue, weakness	Hospitalized
N	50	F	F	Levo/Moxi	During moxi	Myasthenia	Recovered after drug dc'd
N	51	M	D	Cipro	2 days	Leg, back weakness	Unknown
N	55	M	D	Levo	5 days	Progressive weakness	Hospitalized
Y	58	F	F	Cipro	2.5 days	Exacerbation	Death (cardiac arrest)
–	59	F	D	Levo/Cipro	During tx	Arm weakness	Not serious
N	69	M	F	Cipro	9 days	Myasthenia	Hospitalized
–	75	F	D	Cipro	3 days	Arm weakness	Unknown
–	76	M	D	Oflox/Cipro	During tx	Arm weakness	Unknown
N	79	M	D	Cipro	1st dose	Weakness, difficulty standing	Sx resolved
N	83	M	D	Cipro	8 days	Knee weakness	Unknown
N	88	M	D	Levo	During infusion	"Myasthenia gravis"	Hospitalized, intubated

Hx = history of myasthenia gravis
Source: D = domestic; F = foreign
Sx = symptoms experienced

Table 10. MACROLIDES NEUROMUSCULAR JUNCTION DYSFUNCTION (N=27)

Hx	Age	Sex	Source	Drug	Onset	Sx	Outcomes
N	–	F	D	Azithromycin	3 days	Resp. distress	Intubation, plasma exchange
Y	–	F	D	Azithromycin	2 days	Resp. fatigue	Intubation, plasma exchange
Y	–	F	D	Azithromycin	36 hours	"Flare"	Hospitalized, prednisone inc.
–	–	–	D	Clarithromycin	–	Unknown	Unknown
N	–	F	D	Azithromycin	1 day	Muscle "relaxation," couldn't walk, fell	Not serious
–	–	F	D	Azithromycin	–	Leg & arm weakness, numbness	Not serious
Y	–	–	D	Azithromycin	–	Exacerbation	Required intervention (?)
N	12 m	F	D	Azithromycin	2 days post tx	Leg weakness	Not serious
N	14	F	D	Azithromycin	3 days post tx	Arm weakness	Not serious
Y	15	F	D	Erythromycin	1st dose (IV)	Acute respiratory failure	Hospitalized
N	45	M	D	Clarithromycin	1 day	Leg pain, weakness, difficulty walking	Sx resolved after drug dc'd
N	47	F	D	Azithromycin	1 day	Weak knees, legs	Not serious
N	47	F	D	Azithromycin	–	Arm weakness	Not serious
N	55	F	D	Azithromycin	1 day	Leg weakness	Not serious
N	55	M	D	Clarithromycin	5 days	Weakness, difficulty walking	Hospitalized, improved after drug dc'd
N	57	F	D	Azithromycin	3 days	Hand weakness	Not serious
N	57	M	D	Azithromycin	–	Left facial weakness, difficulty swallowing	Diagnosed with MG; underwent thymectomy
N	62	F	D	Azithromycin	1st dose (IV)	"Myasthenia gravis reaction"	Rx with pyridostigmine
–	70	–	D	Azithromycin	–	Leg weakness	Not serious
N	71	F	F	Azithromycin	8 days post tx	Eyelid weakness, diplopia, general weakness	Hospitalized
N	71	F	D	Azithromycin	1 day post tx	Leg weakness	Not serious
Y	72	M	D	Azithromycin	–	Exacerbation, generalized weakness	Not serious
N	75	M	D	Azithromycin	After each dose	Weakness	Not serious
N	81	F	D	Clarithromycin	12 days	Weakness	Hospitalized, recovered after drug dc'd
N	81	M	F	Clarithromycin	5 days	"Massive myasthenia"	Hospitalized, cannot stand on feet
N	81	F	D	Azithromycin	5 days	Numbness, leg weakness	Not serious
N	85	F	D	Azithromycin	1 day	Weakness, difficulty moving	Not serious

Hx = history of myasthenia gravis
Source: D = domestic; F = foreign
Sx = symptoms experienced

SEARCH RESULTS (cont.)

Riluzole

Twenty unduplicated cases were retrieved, four of which were excluded (two cases of riluzole overdose, a case of fentanyl overdose, and a case of cardiac failure secondary to pericarditis). In all cases, except one not stated, riluzole was used in the treatment of ALS. All but two of the cases were foreign reports, primarily from Japan (eleven). The cases involved nine males and seven females, ranging in age from 47 to 76 years (mean—62.4 years, median—63 years). None of the patients were taking telithromycin or a macrolide antibiotic. All of the cases were reported as death secondary to respiratory failure, primarily noted as consistent with progression of ALS. In one case, the patient was diagnosed with myasthenia gravis and is described below.

Case# 3415521; ISR# 3436620-0; Mfr.# JP01-03241 (Japan)—A 75–year–old female patient was given riluzole (100 mg daily per os) from April 12, 1999 to December 09, 1999 for treatment of amyotrophic lateral sclerosis (diagnosed on April 1997). On , antirex (edrophonium chloride) test was negative. On , she developed double vision when watching television. Apparent daily variation of this symptom was not observed. Extraocular muscle paresis was not observed. On , apparent extraocular muscle paresis was observed by the doctor (with no other clinical changes). On brain magnetic resonance image and cerebrospinal fluid test were normal. However, marked facial muscle weakness and muscle weakness of extremities were observed. On , she was admitted to hospital. Daily variation of the symptom of upper extremity muscle weakness was observed. Based on a positive result of antirex test and weaning phenomenon (electromyogram), myasthenia gravis was diagnosed and anti-cholinesterases were administered (NOS), while respiratory condition gradually deteriorated. Aggravation of myasthenia gravis was suspected. Artificial respiration was not used following the patient's will. Immuno-globuline (IV) was also given for treatment of myasthenia gravis. The respiratory failure aggravated and the patient died on . . . . Abnormal value of antiacetylcholine antibody was observed in blood examination (80 nmol/l, normal value <0.2 nmol/l).

FINDINGS

Visual Adverse Events

Using the raw data, of the approximately three million reports in the AERS database, about 1% of the total are reports of visual adverse events (using the MedDRA terms Vision Disorders [HLGT] and Neurologic Visual Problems NEC [HLT]). Of the drugs used in this search, azithromycin and clarithromycin returned the most reports (260), but they also had the most total number of reports in AERS (17,512). The percentage of visual adverse event reports of their total number of reports in AERS was 1.5%, comparable to the percentage seen across the entire AERS database for all drugs.