Contrast this to ethambutol and voriconazole, which had 181 reports but which represented about 19% of their total. This suggests a higher propensity for ethambutol and voriconazole to be associated with visual adverse events, which are well noted in their labeling.

Visual adverse event reports represented 0.7% of all amoxicillin/Augmentin® reports, 2.7% of all gatifloxacin/levofloxacin/moxifloxacin reports, and 2.9% of all doxycycline reports. These percentages appear to reflect how these drugs are labeled—not labeled for amoxicillin/Augmentin®, labeled for the fluoroquinolones, and indirectly labeled for doxycycline (although vision disorders are not specifically stated, benign intracranial hypertension, which can result in visual abnormalities, is listed and many of doxycycline's reports were associated with this condition).

Myasthenia gravis

The results (from Tables 7 – 10) indicate that myasthenia gravis, myasthenic syndrome, and myasthenia gravis–like reactions have occurred infrequently with the selected drugs. Of the 52 total cases, 21 (about 40%) were specifically described as myasthenia gravis or myasthenia gravis–like (the remainder were typically described as weakness). About one-half of these were exacerbations in patients with a history of myasthenia gravis. Ciprofloxacin, erythromycin, and the aminoglycosides have labeling that addresses this issue, either in the Precautions section (erythromycin, gentamicin, tobramycin), or the Adverse Reactions section (ciprofloxacin).

Riluzole

The issue as to whether telithromycin would have an additive myasthenic effect in patients taking riluzole cannot be answered with the available AERS data. Out of the 16 cases of respiratory failure retrieved, none involved the concomitant use of telithromycin and only one case had a diagnosis of myasthenia gravis.

The mode of action of riluzole is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors. Due to its blockade of glutamatergic neurotransmission, riluzole also exhibits myorelaxant and sedative properties in animal models at doses of 30 mg/kg (about 20 times the recommended human daily dose).[1] The mechanism by which telithromycin could exacerbate myasthenia gravis is unknown.[2] The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation. In humans, cytochrome P450 1A2 is the principal isozyme involved in N-hydroxylation. *In vitro* studies predict that CYP 2D6, CYP 2C19, CYP 3A4 and CYP 2E1 are unlikely to contribute significantly to riluzole metabolism in humans.[1] It is estimated that approximately 50% of telithromycin's metabolism is mediated by CYP 450 (3A4) and the remaining 50% is CYP 450 independent.[3] Therefore, it is unlikely a pharmacokinetic interaction would result in an additive effect.

SUMMARY

The results presented are for informational purposes only to provide a perspective as to the degree to which adverse visual events (broadly defined) and myasthenia gravis have been reported for a sampling of currently marketed antibiotics that could serve as comparitors to telithromycin. 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. As such, these data should not be used outside of the context of their intended purpose as background information.

/S/

Ronald Wassel, Pharm.D.

Concur /S/

Melissa Truffa, R.Ph.
Team Leader

References

1. Rilutek Prescribing Information, Aventis Pharmaceuticals, May 2003.
2. EMEA public statement. Precaution regarding use of telithromycin (Ketek™) in patients with myasthenia gravis. April 23, 2003. EMEA/8837/03. Retrieved March 24, 2004 from http://www.emea.eu.int/pdfs/human/press/pus/883703en.pdf
3. Proposed Ketek Prescribing Information, Aventis Pharmaceuticals, 2003.

cc:
NDA # 21-144
HFD-520 Division File / Alexander / Cooper / Milstein
HFD-430 Avigan / Truffa / Kang / Chron / Drug

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/s/

Ronald Wassel
3/30/04 11:10:39 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/30/04 12:28:46 PM
DRUG SAFETY OFFICE REVIEWER

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MEMORANDUM

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

DATE: March 11, 2004

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

VIA: Judit Milstein, Regulatory Health Project Manager,
Division of Anti-Infective Drug Products, HFD-520

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.S.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review Patient Information for Ketek (telithromycin) Tablets, NDA 21-144

The patient labeling which follows represents the revised risk communication materials for the Ketek (telithromycin)) Tablets, NDA 21-144. It has been reviewed by our Office (DSRCS and DMETS) and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on labeling (PI) submitted by the sponsor on November 18, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

We also have the following comments and recommendations:

1. All patient materials should be written at a 6th to 8th grade reading comprehension level. The reading ease score should be 60% or greater which corresponds with an 8th grade reading level. Approximately 50% of the U.S. adult population functions at a lower literacy level and reads below an 8th grade reading level. The proposed PPI has a Flesch-Kincaid Reading

Level of 10.5 and a Flesch Reading Ease of 46.0 %. To improve these scores, and enhance comprehension to a broader population, including those with lower literacy, we have simplified language, shortened sentences, and removing unnecessary information throughout the document.

2. Do not provide examples of other medications in PPIs unless the list is comprehensive. List the class alone or provide a comprehensive list with all tradenames and generic names. People feel "safe" when their medication is not on a list.

3. The patient is unlikely to receive this patient information unless their prescription is dispensed in unit-of-use packages with the patient information enclosed.

4. Does Ketek have a [redacted] indication? The PI states that [redacted] Ketek should only be indicated for treatment.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

APPEARS THIS WAY
ON ORIGINAL

4 Draft Labeling Page(s) Withheld

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/s/

Jeanine Best
3/11/04 12:54:12 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/11/04 01:30:23 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Office of Drug Safety

Memo

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

From: Marci Lee, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Denise Toyer, PharmD.
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Judit Milstein
Project Manager, Division of Anti-Infective Drug Products, HFD-520

Date: February 23, 2004

Re: ODS Consult 02- 0181-1; Ketek (Telithromycin) Tablets; NDA 21-144

This memorandum is in response to the January 21, 2004 request from your Division for a re-review of the proprietary name, Ketek. The submission dated November 18, 2003 included proposed insert labeling, patient package insert labeling, container labels and carton labeling for review.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Ketek since we conducted our initial and follow-up reviews dated August 24 2000, February 23 2001, October 22, 2002, and November 13, 2002 that would render the name objectionable. In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, Ketek , acceptable from a promotional perspective.

In the review of the labels and labeling of Ketek, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user errors. Additionally, DMETS notes that several recommendations for the labels and labeling from previous consults have not been addressed. They are also included in the recommendations below.

A. GENERAL COMMENTS

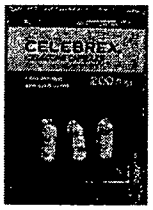
1. Include the dosage form ("Tablets") in the established name.

2. Since the usual dose is 800 mg, [redacted] to minimize medication errors.

B. BLISTER CONTAINER LABEL (10 Tablets)

There is potential for confusion with the blister container label. While, the unit dose blister contains two tablets, it reads "400 mg". Some may think that two tablets are equal to 400 mg total instead of each tablet containing 400 mg (for the 800 mg dose). See below for a similar error published by ISMP in August 2002. Revise the label so that it accurately reflects that each tablet contains 400 mg.

http://www.ismp.org/MSAarticles/Calendar/Aug02.htm#Aug21
Speaking about drug sample packaging, an RN who works in patient safety wrote to tell us about sample packages of **CELEBREX** (celecoxib) that she received recently from her rheumatologist along with a prescription for Celebrex 200 mg BID. The outside carton of each sample pack states "Celebrex 200 mg." This made her think that each package contained 200 mg. But when she opened the box, there were 3 capsules on a blister card that also stated "200 mg." She felt that she needed more information to know whether she should take three capsules for a 200 mg dose, or just one capsule. She called the doctor's office and they said that they are often asked the same question. Many of this doctor's patients are seniors who, although unsure, may not call to clarify the dose. In fact, we confirmed this when we checked with Pfizer. A drug information professional there told us that they have, in fact, received reports of overdoses where 600 mg was taken. Even so, the company has not changed the label since this was first reported! The nurse correctly warned that, "This inappropriate sample packaging may be overdosing many people." We asked the company to take steps to change the labeling immediately and we notified FDA. A photograph appears with this week's issue on our web site.



C. CONTAINER AND CARTON (Ketek Pak 10 Tablets)

1. Post-marketing experience with another antibiotic in a similar packaging configuration includes a report where a patient administered the entire contents of the container in one day rather than five days. We therefore recommend that [redacted] be emphasized on the product labeling. The "Directions For Use" on the inside panel should be revised as follows:

   Take two tablets (at the same time) once a day for 5 days

2. Increase the font size of [redacted] on the container to [redacted].

3. Delete the proprietary name from the packaging configuration (i.e., Ketek Pak). This will be consistent with other antibiotics that use this type of packaging configuration (e.g., Zithromax Tri-Pack).

D. PATIENT INFORMATION

DMETS' recommendations for the proposed patient package insert have been forwarded to the Division of Surveillance, Research, and Communication Support in the Office of Drug Safety and will be incorporated into their review will follow at a later date.

In summary DMETS does not have any objections to the use of the proprietary name Ketek. Additionally, DDMAC finds the proprietary name Ketek acceptable from a promotional perspective. DMETS recommends implementation of the label and labeling revisions outlined above. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Marci Ann Lee
3/3/04 10:23:18 AM
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Denise Toyer
3/3/04 10:40:20 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/4/04 07:36:39 AM
DRUG SAFETY OFFICE REVIEWER

DATE: November 20, 2002

FROM: Cynthia Kornegay, Ph.D., Epidemiologist
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Toni Piazza-Hepp, Pharm.D., Deputy Division Director
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THROUGH: Julie Beitz, M.D., Division Director
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Office of Drug Safety

Anne Trontell, M.D., M.P.H., Division Director
Division of Surveillance, Research, and Communication Support, HFD-410
Office of Drug Safety

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

SUBJECT: Review of Risk Management Plan for Telithromycin (Ketek) for Aventis Pharmaceuticals, Inc.

PID#: D020431

NDA#: 21-144

Executive Summary

The purpose of this document is to review and evaluate the risk management program (RMP) submitted for telithromycin. This plan is a broad outline of an RMP. While the sponsors do attempt to address how the plan will work, most of the details necessary to assess the potential for the plan's success or failure are not included. For example, the adverse events of interest are not well described, and no descriptive epidemiology from the safety trials is included. The sponsor intends to collect data on adverse events, but the particular data elements are not described, and no sample surveys or questionnaires are included. Similarly, an education program is briefly described, but no materials or sample web pages are provided. The sponsor proposes the use of the [redacted] database to monitor adverse events and compliance with the safety profile, however it is likely that many events of interest would not be detected by this data resource, due to both its limitations and the rarity of the adverse events of interest.

Finally, the plan does not describe any connection between the risk assessment of patients and drug dispensing. In the absence of this relationship, it is highly unlikely that this plan will be able to manage or control the risk of any of the adverse events associated with this drug. There is no attempt made on the sponsor's part to evaluate the overall success of the plan and no consideration of how flexible the goals or components would be if the risk profile of telithromycin changes. The sponsors do not include a timetable estimating how long it will be until the plan is operational and how long after until results are available.

In our opinion, this is not a viable RMP, and will not achieve the goal of managing the risks associated with telithromycin. Given the disparate risks of blurred vision, QT prolongation, cutaneous vasculitis, and elevated hepatic transaminase levels, it is unlikely that a single process or component will be a sufficient management tool. In addition, since blurred vision and QT prolongation are not well characterized or understood given the available safety data, these outcomes may not be manageable using current processes. If the sponsor refines the risks to be managed, provides additional details and defines some sort of connection between the components and drug dispensing, the proposed RMP might become workable.

I. Introduction

The document is divided into eight sections: Introduction, Definition of Risk or Adverse Outcomes, Stated Goals of RMP, Specific Components of RMP, Linkage, Feedback, Summary, and References. Dr. Staffa will address issues concerning the proposed data resources, and Dr. Piazza-Hepp will address the proposed educational program. Dr. Kornegay will evaluate the remainder of the RMP.

II. Definition of Risk or Adverse Outcomes

RMP Summary:

The sponsor broadly defines the risks associated with telithromycin in the safety profile of the Background section of the RMP. Aside from gastrointestinal and neurologic events (diarrhea and headache) that are usually associated with antibiotics, there are four adverse events of particular interest:

1. Transient blurred vision
   This occurred in less than 1% of subjects, and the sponsor describes the event as "well characterized". The sponsor did not find evidence of serious eye effects in further studies designed to determine possible mechanisms for this event.
2. Cutaneous vasculitis
   "Isolated" cases of this occurred in phase III trials.
3. QT prolongation
   A mean change of 1.5 milliseconds was observed in clinical trials. In the overall study, an excess of cardiovascular events or deaths was not found.
4. Hepatic transaminase elevation
   Elevations greater than three times the upper normal limit occurred infrequently in clinical trials. No cases of drug-related fulminant hepatic failure, injury leading to transplant, or death were observed.

FDA Reviewer Comments:

Two basic assumptions of any risk management program are:

1. The risk involved can be characterized in terms of a particular disease, condition, or outcome, and
2. An individual's chances of this risk occurring can somehow be minimized or prevented with risk management intervention.

To properly assess the ability of the proposed plan to mitigate the risk of these adverse events, it is essential to have as complete a characterization of the adverse events as possible. For example, did any of the events occur more often in a particular gender or age group, or for a specific indication? What was the average time since administration and time on therapy before these events occurred? Were there any comorbid conditions or concomitant medications that may have contributed to these events? Did any of the events require a doctor's office visit or hospitalization? In particular, the transient blurred vision events should be very well described in terms of the demographics of the population that was preferentially affected (if any), the degree of impairment, and the length of time the vision disturbance lasted. If there are no patterns or trends evident in the occurrence of the event, that should also be noted.

In the submitted proposal, the sponsor does not provide sufficient detail concerning the clinical presentation and severity of the adverse events listed. There is no description of the duration or severity of blurred vision.. No information at all is provided for the cases of cutaneous vasculitis. The mean lengthening of the QT interval is given, but there are no further details on the clinical implications of this finding. Finally, the hepatic transaminase elevations are not adequately described. Although, as the sponsor states, no cases of hepatic failure, transplant, or death were observed, further communication with the division revealed that two cases did require a biopsy, and there was a third case where a biopsy was recommended but not performed[1].

A clear and detailed definition of the risks of interest is necessary to address the second assumption, which is that the risk can be managed. The sponsor fails to describe any of the factors associated with or that contributed to the adverse events. Because of this, it cannot be determined if the risks of these events can be evaluated or managed effectively. A related concern to this is the proposed mechanism for managing the risks. In some cases, particularly where the RMP is focused on managing a single risk or a set of closely related outcomes, a single process or procedure is presented as being sufficient to address all of the events of interest (e.g., isotretinoin and pregnancy prevention). In this particular instance, however, the four events of interest (blurred vision, QT prolongation, cutaneous vasculitis, and elevated hepatic transaminase levels) do not appear to be related physiologically. Given the wide range of body systems and the severity of the outcomes involved, it may be difficult to develop a single mechanism for controlling all of the risks.

Recommendations:

1. The sponsor should define both the outcomes of interest and the risk factors that contribute to these events as clearly and specifically as possible. For example, the sponsor should propose ICD-9 or other codes to be used in defining events of interest in large databases, where appropriate and provide descriptive statistics of the events and risk factors (e.g., means, medians, and ranges) on cases from the pre-marketing safety studies.
2. The sponsor should clearly state any risk factors that are associated with or that may have contributed to the adverse event in question. For example, demographic factors (age, gender), indication, time on therapy, comorbid conditions, concomitant medications should be described for each adverse event of interest. The relative frequency of the adverse event in the populations at higher risk as compared to the frequency of the event in the rest of the pre-marketing study population should also be analyzed and described. If the occurrences of the event do not follow any particular pattern or trend, that should also be noted.
3. The sponsor should recognize that the consequences and risks for each of the outcomes of interest vary widely, and that a single process or procedure is unlikely to manage these disparate risks effectively.

III. Stated Goals of RMP

RMP Summary:

In the Introduction, the proposal broadly defines the goals as "to detect/manage unexpected and very rare adverse events, to regularly update the telithromycin safety profile, to facilitate access to relevant information for prescribers and patients". The RMP further defines the goals as stated below:

1. To generate hypotheses about risk patterns and searching for deaths and possible serious outcomes for hepatic, cardiac, blurred vision, and vasculitis events
2. To confirm the telithromycin safety profile specifically with regard to rare and serious adverse events of special interest (hepatic, cardiac, death, blurred vision, vasculitis)
3. To be able to offer several innovative venues for the practitioner or patient to receive guidance in the most appropriate use of telithromycin based upon their clinical status, to offer opportunities to obtain quick answers to questions concerning telithromycin use, and to receive necessary information concerning their medical experience with telithromycin in the clinical setting
4. To review prescribing behaviors in order to monitor compliance to safety labeling
5. To evaluate and monitor the impact of the risk communication program

FDA Reviewer Comments:
Ideally, the goals for an RMP should be clearly stated, and should relate directly to diminishing the risks associated with the drug. Furthermore, the goals should be practical and able to be measured in a timely, reliable, objective, and appropriate manner. While the sponsor does list the goals succinctly, none of them relate to actively managing or moderating the chances that these events will occur. The sponsor does not indicate if the RMP is intended to mitigate the risk or to eliminate it entirely. In this sense, the sponsor's proposal is more appropriate for risk surveillance or evaluation than risk management. The goals are practical and can certainly be achieved, however, it is unclear how accomplishing any one of the goals will directly and measurably relate to reducing the risk of any of the adverse events. For example, what types of hypotheses will be generated? How will these ideas reduce the risk of any of the outcomes? What kind of objective measure will be used to determine if the telithromycin safety profile is "confirmed" or not? How will offering telithromycin information and guidance in several formats ensure that practitioners understand and apply it appropriately? How will a review of the prescribing behaviors directly reduce the risk, and how will the success of this goal be evaluated? The final goal, evaluating and monitoring the risk communication program, is the clearest and most objective, but it is unclear how that will directly relate to reducing the risk of the adverse events of interest.

Recommendations:
1. The sponsor should relate the RMP goals directly to reducing the risk of the adverse events in question.
2. The goals should be able to be measured in a timely, reliable, objective, and appropriate manner.

IV. Specific Components of RMP

RMP Summary:
In the introduction, the sponsor outlines four major steps: "aggressive" pharmacovigilance, monitoring of known risks and unexpected signals, a risk communication and education program, and monitoring of safety labeling compliance. In the risk management section, the sponsor expands on each of these steps.

A. "Aggressive" pharmacovigilance

The sponsor proposes to attempt to obtain all available data for adverse events of interest (hepatic, cardiac, blurred vision, and vasculitis) and other unexpected adverse outcomes. Furthermore, an "event of special interest" questionnaire will be used to collect detailed data from reporting healthcare

professionals, and attempts will be made to follow all events to resolution. Periodically, an aggregate safety analysis of all events will be generated and forwarded to the FDA, including a critical assessment of events of special interest. Finally, the sponsor will continue to monitor the reported adverse events for possible new safety signals.

B. Monitoring known risks and unexpected signals

The sponsor will monitor events using retrospective cohort studies in the [redacted] database, which [redacted] They plan to compare the claims experience of individuals treated with telithromycin versus those treated with several comparator drugs. The sponsor estimates that within one year after the addition of telithromycin to the insurance plan's formulary, they will be able to detect a 2.5-fold increase in risk, assuming a background incidence rate of 10 per 100,000 prescriptions for all adverse events. In addition, within 2½ years, there will be sufficient power to detect a 30% increase in risk, assuming a 1-sided test with alpha=0.05 and an equal number of patients in the telithromycin and comparator groups.

Adverse events of special interest will be identified from diagnosis codes, as [redacted] are not available in the [redacted] database. To address the potential for misclassification, the sponsor intends to use relative rate and incidence statistics rather than absolute statistics. In addition, the sponsor will focus primarily on events that resulted in hospitalization. The incidence of non-rare adverse events and those that do not result in hospitalization will be monitored, although the sponsor does not specify the method. To put the proposed analyses and results into context, the sponsor will tabulate the demographics and associated morbidity of patients treated with telithromycin.

C. Risk communication and education

The proposed risk communication and education program has three goals: to provide innovative venues for patients and providers to receive guidance regarding appropriate use of telithromycin with respect to their clinical situation, to offer the ability for patients and providers to receive quick answers to questions regarding telithromycin use, and to receive necessary information concerning medical experience with telithromycin. To achieve these goals, the sponsor proposes to hold programs and seminars for providers, specifically regional scientific education programs. In addition, a Medical Information Service will be available via telephone and Internet to answer questions concerning telithromycin use in particular clinical settings. This service will be available to patients and providers 24 hours a day, and reachable through a telephone number to be provided in the label, PDR, web sites, and through sponsor representatives. Finally, the sponsor will create a telithromycin web site, which will give patients and providers access to an electronic label, the Medical Information Service, an algorithm to determine appropriate clinical use of telithromycin, and questions and answers to all queries generated in telithromycin programs and seminars.

D. Monitoring safety labeling compliance

In addition to monitoring the known risks and unexpected signals, the sponsor also proposes to monitor provider adherence to telithromycin safety labeling using the [redacted] database.

FDA Reviewer Comments:

Each of the proposed components will be commented on separately, and recommendations will be made at the end of each section and at the end of the entire section.

A. Aggressive pharmacovigilance

The sponsor proposes an enhanced information gathering process that will aid in achieving the goals of hypothesis generation and completing the safety profile (goals 1 and 2). If the appropriate information is collected, this step may also provide information for goals 4 and 5 concerning the prescribing behaviors and compliance with safety labeling. While the sponsor provides an outline of the process of how the additional information will be gathered and from whom, no description of the additional details to be collected is provided. The sponsor mentions an "event of special interest" questionnaire that will be used to gather this data, but a sample of the form is not provided, nor is a list of specific data elements to be collected.

A second concern is the person from whom the sponsor intends to get this additional information. In particular, while the healthcare provider may be the most appropriate person to provide data for QT prolongation, cutaneous vasculitis, and hepatic transaminase levels, it is not clear that this is the case for blurred vision. Patients may not see the connection between telithromycin and blurred vision, and therefore not tell their healthcare provider about it. For blurred vision, if appropriate analysis variables can be determined, it would seem that the patient could provide more accurate information than the provider.

Finally, the sponsor does not provide any information on the value added from this type of pharmacovigilance. It is not clear if this process will build upon the sponsor's existing pharmacovigilance system, or will be a separate entity. An aggregate safety analysis is alluded to, but the sponsor does not specify what types of analyses will be performed, or how this is different from what is already required for postmarketing pharmacovigilance. The sponsor does not provide information on what will constitute a new signal or a change in the safety profile of telithromycin.

Recommendations:

1. The sponsor should describe in detail the data that will be collected for each adverse event of special interest that is in addition to what is required by postmarketing pharmacovigilance.
2. The sponsor should ensure that the information is collected from the appropriate individual (provider or patient) based on the risk being assessed.
3. The sponsor should describe what additional value this type of pharmacovigilance will add to the RMP
4. The sponsor should define what level(s) of occurrence relative to the pre-marketing safety trials will prompt additional actions. The sponsor should also define what statistical analyses will be done that are beyond what is already required for postmarketing pharmacovigilance.

B. Monitoring known risks and unexpected signals

The use of the [redacted] database appears to provide large numbers of patients for observation of the effects of telithromycin and other comparator antibiotics. However, it is not clear how many patients might be prescribed telithromycin in its early marketing, because the sponsor does not discuss the factors that would influence its addition to the formulary of the health plans. Health plans wait several months or more after a product's launch before adding it to the formulary. They may wait for internal or external evaluations of the product's risk, benefits, and costs in comparison to other available therapies to assist them in their decision-making process. Since [redacted], the date of addition to

the formulary could differ for each plan, and cause a rather lengthy lag time before exposed cohorts could be assembled.

Little information is provided about the numbers and types of patients covered in the — database. No information is provided about the number of patients with prescription drug coverage, the geographic and demographic distributions of the covered populations nor the "turnover" of participants within these health plans. All of these factors will affect the number and type of telithromycin users ultimately available for study

The unavailability of medical records in the — database is also problematic and will lead to misclassification of outcomes in both the telithromycin and comparator cohorts. If this misclassification of disease is nondifferential between cohorts, as suggested by the sponsor, it will bias results towards the null (no association), and will occur to different degrees for the different outcomes under study. Previous studies in the medical literature suggest that medical records are necessary for studying acute liver disease in claims databases[2]. In addition, a recent ODS examination of Medicare inpatient claims and medical records found that past medical events such as a history of liver failure may be coded simply as "liver failure" and so mistakenly appear to be a current diagnosis.

Given that there may well be differences in the characteristics of the patient populations prescribed telithromycin and the other comparator drugs, the misclassification may not be nondifferential in nature, but rather more pronounced in one cohort than another. This would cause the results to be biased in a less predictable fashion and thus undermine the study's validity. Careful characterization of the patient populations in each cohort would be necessary to even consider such effects.

At the very least, the investigators should provide evidence that would support using only administrative claims for ascertainment of outcome – e.g., do they have data from previous studies to suggest that ICD-9 codes for acute liver failure are valid markers for actual diagnoses of acute liver failure, as validated by patient medical record review? If so, which codes appear to be most valid? Since validity will vary by diagnosis, this question must be addressed for each proposed study outcome. For example, although ICD-9 codes for agranulocytosis[3] and cardiac arrest[4] have been demonstrated to be valid markers for those actual diagnoses in medical records, the same is not true for aplastic anemia[5] and ventricular arrhythmias[4], where only 25% or fewer of claims codes actually correlated with a true diagnosis. Additionally, at least one of the outcomes, "blurred vision" will be poorly identified using only claims data, since it is transient, not likely to come to medical attention or result in hospitalization, and not clearly defined using ICD-9 codes. A more appropriate design for examining this outcome, which likely involves direct contact with patients, has not been included.

The statements that suggest that the number of patients exposed to telithromycin within a year of marketing will allow for estimations of a 2.5 fold increase in risk are based on assumptions for which no justification is provided. Further detail that would allow an appropriate evaluation of these estimations would be required to conduct a thorough evaluation, including the estimated number of patients exposed to both telithromycin and comparator drugs, and a justification for the background rate of events assumed. This would be predicated upon a thorough understanding of the impact of formularies on drug availability as described above.

The sponsor makes an assumption that all adverse events will occur at a background rate of 1 in 10,000. This assumption is not supported by any analyses or documentation. A literature search revealed two potential problems with this assumption – 1) the adverse events of interest do not have specific ICD-9 codes, and so are

not easily identifiable in claims databases, and 2) the background rates for these adverse events, when available, are much lower than the sponsor assumed. Background rates could not be found for blurred vision, elevated hepatic transaminase levels, and lengthened QT intervals. A background rate of between 0.04 and 0.25 per 10,000 was found for small vessel vasculitis[6,7]. This rate is likely an overestimate, since cutaneous vasculitis is one of many conditions in this category, and does not have its own ICD-9 code.

Finally, no information is provided as to whether the sponsor has experience using [redacted] data for epidemiologic studies, nor have any citations of any published pharmacoepidemiologic studies using these data, without medical record access, been included.

Recommendations:

1. The sponsor should select the most appropriate database for monitoring known risks and expected signals. Ideally, this data resource would have access to medical records, laboratory values, and EKG results for a large proportion of the individuals in the target population.
2. The sponsor should provide background information and demographics on the data resource chosen, particularly in relation to the target population of telithromycin, as determined by its labeled indications.
3. The sponsor should ensure that the method of monitoring would be sensitive enough to detect new or excess cases of the adverse events of interest.
4. The sponsor should obtain information on the most likely scenario for inclusion of telithromycin by health plan formularies, based on marketing information or experience of previous products, and use this information for realistic estimation of sample size accrual over time. This should then be used together with known background rates for the events of interest to calculate more appropriate estimates of statistical power.

C. Risk communication and education

Although an evaluation plan, using the [redacted] database, is alluded to, no detail is provided. An essential part of the RMP is an evaluation of the program, with appropriate detail and documentation. Although the sponsor specifies that a phone number will be included in the labeling, there is no indication of how the patients will gain knowledge of the benefits and risks of telithromycin or how they will know of the existence of these educational services. In addition, without further documentation and detail, the adequacy of the proposed means of communication (various website materials or other educational pieces) cannot be evaluated.

One possibility is for the sponsor to develop a patient package insert (PPI) or medication guide (MG). If the sponsor chooses to do this, a draft should be submitted to the Agency for review as soon as possible. If a PPI is the mechanism chosen for patient labeling planned by the sponsor, the PPI should use headings in a question and answer format as described for a Medication Guide under 21CFR 208.20. Also, the PPI or MG should be written in lay language at a sixth to eighth grade level. Any additional educational materials intended for patients should also be submitted for review. The sponsor should additionally describe any plans to assess the effectiveness of educational materials directed at patients, through comprehension studies or other means.

Recommendations:

1. The sponsor should provide copies of the actual educational materials for review and comment.
2. The sponsor should specify and describe the target population(s) to receive the material, and should estimate the proportion of the target population that are likely to access the material in each presented format.

3. The sponsor should provide the results of any pre-testing of comprehension for the materials.
4. The sponsor should describe, in detail, how they intend to determine if the materials are being received and understood by the target population(s).
5. The sponsor should provide an estimated timeline for implementing the program, and for evaluating and reporting on the success of the program once it is operational. In conjunction with this, the sponsor should clearly define how the success or efficacy of the program will be measured.

D. Monitoring safety labeling compliance

The sponsor suggests that the — claims database will be used to evaluate the impact of telithromycin dose on risk of adverse events. It has been shown that claims databases often do not provide accurate information on drug dose when compared to medical records [8,9]. The sponsor does not provide any documentation or prior studies that labeling compliance has been or can be accurately measured using this database, nor do they provide any details on how they intend to measure dosage or any other metric for safety labeling.

Recommendations:

1. The sponsor should provide documentation showing that claims databases in general, and the — database in particular, have accurate dosage information and can be used to monitor safety labeling in this manner.
2. The sponsor should provide a detailed plan on how they specifically intend to monitor safety labeling.
3. The sponsor should provide a timeline estimating how long it will take until the relevant monitoring information is available.

Individually, each of the four steps is an outline of the proposed components of this plan. The sponsor does not provide detail on how each component will work individually and together to achieve the goal of risk reduction. As with the Risk Definition section, the "one size fits all" nature of these components is a concern. Given the wide range of risks and severities, it is not likely that a single survey or questionnaire will be adequate to collect the necessary safety information (the sponsor does not specify if more than one survey or questionnaire will be used to collect data). Likewise, it is also doubtful that a single data resource will be able to perform all of the monitoring and evaluation functions assigned to it in this RMP at an acceptable level.

General Recommendations:

1. The sponsor should consider using separate processes to monitor disparate risks, instead of attempting to use one method to manage them all. For example, a patient registry might be better able to detect blurred vision or elevated laboratory values.
2. The sponsor should ensure that the evaluation of the success of these components is done using the appropriate data resource or resources, and in a timely manner.

V. Linkage

RMP Summary:

There is no description of any explicit link between risk factor evaluation and drug prescribing behavior modification in the RMP.

FDA Reviewer Comments:

An essential element in managing the risk associated with a drug is some sort of explicit link or relationship between the steps in evaluating and/or controlling the risk and the actual drug prescribing or use. This link could be direct, as with the isotretinoin and thalidomide pregnancy prevention programs, or indirect, such as through ads, seminars, newsletters, etc. If there is no direct or indirect relationship between determining a new signal or a change in the frequency of the adverse events of interest with drug prescribing, then there is no "management" of these outcomes.

The proposed RMP does not define or describe any relationship between identifying a new risk factor or changes in the telithromycin safety profile and altering the circumstances in which telithromycin is dispensed. For example, in the thalidomide pregnancy prevention program, confirmation of two effective forms of contraception is required before the drug is dispensed. Likewise, in the clozapine risk management program, confirmation that the patient has not developed agranulocytosis is required for the drug to be dispensed. While these direct forms of control may or may not be necessary in this case, the sponsor should propose some mechanism to update providers, pharmacists, and patients with any changes in the risk profile for telithromycin that could change prescribing or use. This link should be timely, and changes in prescribing should be able to be tracked by some objective and reliable means.

Recommendations:

1. Sponsor should explicitly describe the link between risk factor evaluation and drug prescribing.

VI. Feedback

RMP Summary:

The sponsor proposes to use the — database to measure two specific components of the plan, to monitor the known risks and unexpected signals and to evaluate the compliance with safety labeling. Overall, the sponsor does not propose any mechanism or process to evaluate the plan as a whole.

FDA Reviewer Comments:

In order to evaluate the effectiveness of an RMP, its impact or effectiveness must be measured in a reliable, objective, appropriate, and timely manner. The RMP should include information on how and when the sponsor intends to measure the impact of the program. In addition, the overall RMP should be flexible enough to accommodate, in a timely manner, changes in goals, steps, or linkage in response to this feedback.

The sponsor does not propose any way of assessing how appropriate the proposed processes will be for managing the risks. Additionally, the sponsor does not provide enough information to determine if the proposed mechanisms will be able to provide a timely, reliable and accurate measure risk containment. Because the sponsor provides no detail, there will be no way to assess how effective the plan is once implemented.

Recommendations:

1. The sponsor should provide a detailed plan to evaluate the success of the RMP. The metrics used to evaluate the RMP should be reliable, valid, and objective.

VII. Summary

The proposed RMP is sketchy and incomplete. Neither the adverse outcomes nor their risk factors are well defined or characterized. Additionally, the goals and components of the plan are not directly related to

managing the risk of the outcomes of interest. The proposed database, and the manner in which the sponsor intends to use it, will not be able to capture the non-acute outcomes (blurred vision) or outcomes that do not have a distinct ICD-9 code (blurred vision, elevated hepatic transaminase levels, lengthened QT interval, cutaneous vasculitis). Furthermore, the lack of medical records and laboratory values will make it difficult to detect the blurred vision and elevated hepatic transaminase levels among telithromycin users. Furthermore, given the rarity of these outcomes, it is unlikely that the database will be able to detect any events at all, and, if some do occur, that an analysis will be able to separate the drug-related events from the background population rate.

The sponsor describes an "event of special interest" questionnaire, but do not provide a sample, nor do they provide any documentation of what data will be collected or how successful this method of collection has been in the past. The sponsor states that they will be monitoring adverse events reported with telithromycin for unexpected new signals or a change in frequency of the adverse events of interest, but there is no description of what will constitute either a potential new signal or a substantive change in frequency. An educational program is briefly described, but again, no background or supporting materials are provided.

An essential element of risk management is some sort of direct or indirect relationship between the components and changes in drug use or prescribing. The sponsors do not propose any sort of link, whether through patient or provider questionnaires, laboratory testing, or indirectly through ads or company presentations. Without this link, it is not possible to "manage" or control any of the risks associated with telithromycin. The sponsors do not provide any time estimates on how long it will take this plan to become functional, and once in operation, how long it will be until any results will be available. Finally, the sponsors do not describe any means by which the plan itself can be evaluated.

Following is a list of all of the FDA reviewer recommendations from individual sections of this document.

Definition of Risk or Adverse Outcomes

1. The sponsor should define both the outcomes of interest and the risk factors that contribute to these events as clearly and specifically as possible. For example, the sponsor should propose ICD-9 or other codes to be used in defining events of interest in large databases, where appropriate and provide descriptive statistics of the events and risk factors (e.g., means, medians, and ranges) on cases from the pre-marketing safety studies.
2. The sponsor should clearly state any risk factors that are associated with or that may have contributed to the adverse event in question. For example, demographic factors (age, gender), indication, time on therapy, comorbid conditions, concomitant medications should be described for each adverse event of interest. The relative frequency of the adverse event in the populations at higher risk as compared to the frequency of the event in the rest of the pre-marketing study population should also be analyzed and described. If the occurrences of the event do not follow any particular pattern or trend, that should also be noted.
3. The sponsor should recognize that the consequences and risks for each of the outcomes of interest vary widely, and that a single process or procedure is unlikely to manage these disparate risks effectively.

Stated Goals of RMP

4. The sponsor should relate the RMP goals directly to reducing the risk of the adverse events in question.
5. The goals should be able to be measured in a timely, reliable, objective, and appropriate manner.

Aggressive Pharmacovigilance

6. The sponsor should describe in detail the data that will be collected for each adverse event of special interest that is in addition to what is required by postmarketing pharmacovigilance.
7. The sponsor should ensure that the information is collected from the appropriate individual (provider or patient) based on the risk being assessed.
8. The sponsor should describe what additional value this type of pharmacovigilance will add to the RMP.
9. The sponsor should define what level(s) of occurrence relative to the pre-marketing safety trials will prompt additional actions. The sponsor should also define what statistical analyses will be done that are beyond what is already required for postmarketing pharmacovigilance.

Monitoring known risks and unexpected signals

10. The sponsor should select the most appropriate database for monitoring known risks and expected signals. Ideally, this data resource would have access to medical records, laboratory values, and EKG results for a large proportion of the individuals in the target population.
11. The sponsor should provide background information and demographics on the data resource chosen, particularly in relation to the target population of telithromycin, as determined by its labeled indications.
12. The sponsor should ensure that the method of monitoring would be sensitive enough to detect new or excess cases of the adverse events of interest.
13. The sponsor should obtain information on the most likely scenario for inclusion of telithromycin by health plan formularies, based in marketing information or experience of previous products, and use this information for realistic estimation of sample size accrual over time. This should then be used together with known background rates for the events of interest to calculate more appropriate estimates of statistical power.

Risk communication and education

14. The sponsor should provide copies of the actual educational materials for review and comment.
15. The sponsor should specify and describe the target population(s) to receive the material, and should estimate the proportion of the target population that are likely to access the material in each presented format.
16. The sponsor should provide the results of any pre-testing of comprehension for the materials.
17. The sponsor should describe, in detail, how they intend to evaluate if the materials are being received and understood by the target population(s).
18. The sponsor should provide an estimated timeline for implementing the program, and for evaluating and reporting on the success of the program once operational. In conjunction with this, the sponsor should clearly define how the success or efficacy of the program will be measured.

Monitoring safety labeling compliance

19. The sponsor should provide documentation showing that claims databases in general, and the [redacted] database in particular, have accurate dosage information and can be used to monitor safety labeling in this manner.
20. The sponsor should provide a detailed plan on how they specifically intend to monitor safety labeling.
21. The sponsor should provide a timeline estimating how long it will take until the relevant monitoring information is available.

Specific Components of RMP – General recommendations

22. The sponsor should consider using separate processes to monitor disparate risks, instead of attempting to use one method to manage them all. For example, a patient registry might be better able to detect blurred vision or elevated laboratory values.
23. The sponsor should ensure that the evaluation of the success of these components is done using the appropriate data resource or resources, and in a timely manner.

Linkage

24. The sponsor should explicitly describe the link between risk factor evaluation and drug prescribing.

Feedback

25. The sponsor should provide a detailed plan to evaluate the success of the RMP. The metrics used to evaluate the RMP should be reliable, valid, and objective.

VIII. References

1. Personal communication with Dr. David Ross, M.D. on 11/01/2002
2. Carson JL, Strom BL, Duff A, Gupta A, Shaw M, Das K. The feasibility of studying drug-induced acute hepatitis with use of Medicaid data. Clin Pharmacol Ther 1992;52:214-19.
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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 9/10/02	**DUE DATE:** 10/22/02	**ODS CONSULT #:** 02-0181

TO:

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

THROUGH:

Judith Milstein
Project Manager, Division of Anti-Infective Drug Products
HFD-520

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

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

SUMMARY: In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed container labels and carton labeling for "Ketek" for safety issues relating to possible medication errors.

DMETS RECOMMENDATION:
DMETS recommends implementation of the labeling revisions outlined in section II of this review to minimize potential errors with the use of this product. The name, Ketek, must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

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Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY LABELING REVIEW

DATE OF REVIEW: October 16, 2002

NDA NUMBER: 21-144

NAME OF DRUG: Ketek (Telithromycin) Tablets 400 mg

NDA HOLDER: Aventis Pharmaceuticals Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective Drug Products (HFD-520) for a safety assessment of the labeling for "Ketek".

The proprietary name was reviewed by DMETS and found acceptable (see Consult 00-0101). At the time of initial review, labeling recommendations were provided by DMETS. The sponsor has submitted revised container labels and carton labeling for review and comment.

PRODUCT INFORMATION

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

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

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

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

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

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

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and carton labeling of Ketek, DMETS has focussed on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

Please note that the established name of your product is Telithromycin Tablets. Include the full established name of your product in conjunction with the proprietary name on container labels and carton labeling and in the package insert labeling where required.

B. CONTAINER LABEL (10 tablet blister card and Physician Sample 2's and 10's)

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

2. In recent post-marketing experience with another antibiotic, Avelox, in which the sponsor had a similar packaging configuration, a patient administered the entire contents of the container in one day rather than five days. We therefore recommend the — oe highlighted on the product labeling. The "Directions For Use" on the inside panel should be revised as follows:

   Take two tablets (at the same time) once a day. —

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

   Usual Dosage: Take two tablets once daily for —

C. INSERT

See GENERAL COMMENT and comment 2 under CONTAINER LABEL.

III. RECOMMENDATIONS:

A. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

B. The name, Ketek, with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-7847.

/S/

Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

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MEMORANDUM OF MEETING MINUTES

Meeting Date:	**October 12, 2001**
Location:	**Corp S-300**
Applications:	**IND 55, 283/NDA 21-144**
Drug:	**Ketek (telithromycin)**
Meeting Chair:	**Dr. Janice Soreth, M.D., Acting Division Director**

FDA's Attendees:
Janice Soreth, M.D. -Acting Division Director
Mark Goldberger, M.D., M.P.H. -Division Director (DSPIDP)
Alma Davidson, M.D. -Medical Reviewer
Jenny Zheng, Ph.D. -Biopharmaceutics Reviewer
George Rochester, Ph.D. –Mathematical Statistican
Frank Pelsor, PharmD. -Biopharmaceutics Team Leader
John Alexander, M.D. -Acting Clinical Team Leader
Douglas Throckmorton, M.D. -Deputy Director, DCRDP
Jose Cintron –Project Manager, R.Ph., M.A.

Aventis Attendees:
Steve Cafre, M.D. -Head, US Regulatory
Vijay Bhargava, Ph.D. -Clinical Pharmacology
Stephen Jenkins, Ph.D. -Global Head, Clinical Microbiology
Bruno Leroy, M.D. -Global Clinical Manager
William Pullman, M.D., Ph.D. -Global Head, Clinical Pharmacology
Sol Rajfer, M.D. -Head, Global Clinical
Divakar Sharma, Ph.D. -Therapeutic Area Head -Statistics
Kristen Sharma, M.D. -Global Drug Safety Manager
Bill Stager, Ph.D. -Statistics
Thomas Watson -Regulatory

PURPOSE:

The purpose of the meeting was to obtain the Division's concurrence on the sponsor's overall plan to address the issues raised in the Ketek approvable letter. Aventis is seeking registration of Ketek for the treatment of CAP (including ERSP and/or PRSP), AS (including ERSP and/or PRSP) and AECB.

The agenda of the meeting followed the points as presented in the Aventis briefing document (Serial Submission # 178, dated September 12, 2001).

DISCUSSION AND RECOMMENDATIONS: A summary of discussions and conclusions reached at the meeting are listed below:

1. The Division accepted Aventis' overall package of additional studies, designed to address the issues raised in the approvable letter.

2. Concerning community acquired pneumonia (CAP) due to *S. pneumoniae* resistant to macrolides (ERSP) or penicillin G (PRSP), the Division recommended that Aventis make sure to have a large enough number of patients with associated pneumococcal bacteremia and/or accepted severity criteria, to enhance the benefit/risk profile of Ketek. However, the

Division recognized the difficulty of studying severe cases with an oral anti-infective as opposed to an intravenous anti-infective agent. The granting of a resistance claim will be dependent upon the cure rate as well as on the severity of disease of the patients. The Division advised Aventis to try to strengthen the benefit side of the benefit/risk profile of Ketek in order to offset potentially undesirable/unanticipated adverse safety signals.

3. Although, the Division stated that urinary antigen test data do not add much additional information, the Division would still consider these data along with the sputum culture data.

4. The Division agreed with Aventis' proposal that some of the ERSP and PRSP cases could come from Japanese studies. The agency added that for these Japanese cases, Aventis should provide the CRFs (translated in English).

5. Regarding pneumococcal resistance (PRSP, ERSP), the Division expressed significant interest in the ERSP data. The Division requested assurance that the mechanisms of resistance for *S. pneumoniae* to macrolides have no impact on the clinical efficacy of telithromycin. The Division stated that the burden of proof for ERSP will be higher than for PRSP and that the Division would be amenable to reviewing additional information on ERSP.

6. The Division noted that the additional program does not include a study in Acute Sinusitis (AS) with an assessment of efficacy in ERSP or PRSP. The Division reiterated that such a claim could be granted only if efficacy was shown in these strains in CAP. The Division indicated that a specific number of PRSP or ERSP in AS needed to achieve this claim in AS is still being discussed internally within the agency to assess whether the numbers of strains in AS presented in the NDA would be sufficient. The Division added that the level of activity as well as the number of PRSP or ERSP would be considered.

7. The Division stated that Aventis proposal was acceptable for the number of isolates to be provided in the amendment for *H. influenzae* and *M. catarrhalis,* in order to obtain the claim for AECB due to these pathogens.

8. The Division stated that there were few patients with atypical pathogens in the NDA database (e.g. regionella pneumophila). Aventis responded that there were 12 patients infected with atypical pathogens in the NDA database (all cured) and that there would be approximately 5 more in the amendment.

9. The Division inquired as to the stability of Ketek in an acid pH and to the effect of inoculum size on the activity of telithromycin. Aventis responded that Ketek is stable in an acid pH as opposed to the stability of macrolides and that the inoculum size effect is negligible. Aventis committed to providing additional information on pH stability and inoculum size effect to the Division.

10. Regarding the agency's original request to recruit 40% of the study patients with CAP (i.e. treated for 7-10 days) in study 3014, the Aventis' proposal to use both CAP and AECB patients to achieve the 40% target for patients treated for 7-10 days was accepted by the agency.

11. The clinical pharmacology program designed to address the Division's concerns regarding the administration of Ketek to patients with renal impairment (1062) and multiple metabolic impairment (1063) was accepted by the agency. The only concern that the Division had was regarding the possibility of dropouts in these studies which would decrease the number of evaluable subjects. The Agency would be looking for 8 evaluable patients per arm in study 1062 and 12 evaluable subjects per arm in study 1063. The Division added that they did not deem the "clarithromycin" arm in study 1063 as necessary. In study 1063, the Division recommended that half of the 12 patients per arm have creatinine clearances at the lower end of the range.

12. The preliminary results of study 1059 (blurred vision study) that were very recently submitted to the agency are yet to be reviewed by Dr. Wiley Chambers (Ophthalmology Division). The Division response to Aventis' proposal, that no additional specialized investigation with respect to blurred vision is necessary, would depend on Dr. Chamber's review. The Division will attempt to receive Dr. Chamber's feedback within 30 days. The agency stated that the final study report for study 1059 should be submitted to the agency as soon as possible. Aventis is targeting submission of the report in November.

13. The Division requested that all new studies to be included in the future amendment use the MedDRA dictionary. The FDA reconfirmed that these data would not have to be integrated with the original NDA data. However, if there were apparent discrepancies between the rates reported in the original NDA versus those in the amendment for particular AE's, there should be an effort to identify whether these differences were real or due to dictionary mappings.

14. In response to the Division's question about the timing of the future amendment to address the Ketek approvable letter, Aventis responded that the target date for submission of the amendment was July 2002.

15. The agency suggested that Aventis have a "pre-NDA" type meeting before the submission of the amendment. The Division agreed to continue the dialogue with Aventis, providing guidance and feedback on data collection to help Aventis submit a package that clearly outlines the risks and benefits of Ketek.

Issues Requiring Further Discussion: None

Minutes Preparer: Jose R. Cintron, R.Ph., M.A.
Senior Regulatory Management Officer

Chair Concurrence: Janice Soreth, M.D.
Acting Division Director

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MEMORANDUM

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

DATE: July 30, 2002

TO: NDA 21-144, Ketek (telithromycin

FROM: Judit Milstein, Regulatory Project Manager

SUBJECT: **Slides from presentation made by Aventis at the meeting held on August 25, 2002**

NDA 21-144 was resubmitted on July 24, 2002, in response to an AE letter dated June 1, 2001. At the meeting held August 25, 2002, the sponsor made a presentation to demonstrate the data entry for Study 4003 and the dataset navigation for Study 3014, both studies part of the resubmission.

Attached to this memo are the slides used by the sponsor during the presentation

Attachment # 1. Overview of Phase 1 and Phase 3 databases and datasets (Studies 3014 and 4003)
Attachment # 2. Study HMR3647/4003, data entry.

Attachment #3. Study HMR3647/4003, data capture

SPONSOR MEETING ATTENDEES

Meeting Date: July 25, 2002 **Time:** 12:00-2:00 p.m.

Location: Corporate Building, Conference Room S-300

NDA/ Name : 21-144/Ketek

Sponsor: Aventis Pharmaceuticals

Type of Meeting: Guidance

Sponsor's attendees

[redacted]	Study 4003 Technical QA Director, [redacted]
Bhargava, Vijay	Head, US DMPK
Bryers, Paul	Project US Regulatory
Caffé, Steve	Head, US Regulatory
Goedde, Michael	Project Data Manager
Hsuan, Alice	Head, Data Management and Biostatistics
Jenkins, Stephen	Project Microbiologist
[redacted]	Study 4003 Technical Project Leader, [redacted]
Lee, Monica	Project CMC
Le Gallo, Christophe	Project SAS Programmer
Leroy, Bruno	Project Leader
Mittnacht, Stewart	Head, Regulatory Submissions Management
Nusrat, Roomi	Project Clinical Director
Pitcher, Julie	Study 4003 Data Coordinator
Sanocki, John	Project SAS Programmer
Sharma, Divikar	TA Head (Anti-Infectives/CV), Bioostatistics
Sharma, Kristen	Project Safety Officer
[redacted]	Study 4003 Study Manager. [redacted]
Stager, Bill	Project Statistician

FDA's attendee's

Janice Soreth, M.D.	Division Director
John Alexander, M.D.	Medical Team Leader
Charles Cooper, M.D.	Medical Reviewer
David Ross, M.D.	Medical Team Leader
Janice Pohlman, M.D.	Medical Reviewer
Thamban Valappil, Ph. D.	Biostatistician
Harold Silver	Clinical Microbiology Reviewer
George Rochester, Ph.D.	Biostatistician
Albert Sheldon, Ph.D.	Microbiology Team Leader
Daphne Lin, Ph.D.	Biostatistics Team Leader
Judit Milstein	Project Manager

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/s/

Judit Milstein
8/8/02 08:45:01 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville, Maryland 20857

PID: D000601

DATE: February 20, 2001

FROM: Douglas N. Shaffer, M.D., M.H.S.
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Sarah J. Singer, R.Ph.
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THROUGH: Kathleen Uhl, M.D.
Acting Director
Division of Drug Risk Evaluation II

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

M. Dianne Murphy, M.D.
Director
ODE 4

Joyce Korvick, M.D., M.P.H.
Chairperson, ODE-IV QT Working Group

SUBJECT: Macrolide Antibiotics and Torsade de Pointes

Confidentiality Statements

1) This document includes IMS data and therefore may not be used outside the FDA without appropriate clearance.
2) This consult includes reference to CardioRenal Division Consult, October 2000.

EXECUTIVE SUMMARY

Findings

I. Torsade de Pointes (TdP) is a rare, potentially fatal cardiac arrhythmia identified with macrolide antibiotics and present in postmarketing spontaneous report data:
   1. Report demographics resemble those associated with TdP in general: an older (mean age = 60 +/- 22 years), female (72%) population.
   2. Erythromycin represents the largest proportion (54%) of reports and strongest TdP data mining signal (8- $\leq$ 16) for macrolide antibiotics as suspect drugs.
   3. Clarithromycin has the greatest crude reporting rate (31 reports/ ——— prescriptions) when considering only domestic, oral-formulation reports and adjusting for drug utilization.
   4. Fatal outcomes represent 9% of the macrolide-associated TdP reports.

II. Polypharmacy, comorbid diseases, and electrolyte abnormalities are prevalent in postmarketing reports of macrolide-associated TdP:
   1. 52% of the reports include concomitant drugs or drug classes recognized to prolong the QT interval.
   2. 35% of the reports include drugs identified as pharmacokinetic drug interactions and withdrawn from the market (astemizole, cisapride, or terfenadine).
   3. Cardiac disease is a common comorbidity (43%) identified in the spontaneous reports.
   4. Hypokalemia or hypomagnesemia are less frequently reported (18%).

III. Limited Torsade de Pointes postmarketing spontaneous reports including both "baseline" and "event" QT data suggest:
   1. Baseline QT is moderately correlated with event QT (r= 0.51).
   2. Baseline QT is linearly related to event QT (p=0.002, R^2 = 0.26) without evidence of a threshold or plateau (quadratic term, p=0.19).

Recommendations

To the extent telithromycin (the first, new ketolide antibiotic structurally and pharmacodynamically similar to macrolide antibiotics) inhibits hepatic metabolism and prolongs the QT interval:

I. Recognition of the potential for QT prolongation and drug interactions must be addressed in the product labeling.

II. [redacted]

III. Continuous accumulation of spontaneous reports is warranted in effort to build the number of observations regarding iatrogenic Torsade de Pointes.

BACKGROUND

Torsade de Pointes (TdP) is a polymorphic ventricular tachycardia related to a pre-existing prolongation of the QT interval. Originating from the French term meaning "twisting of points," TdP is characterized by an apparent helical ventricular tachycardia twisting around the isoelectric line. TdP historically has been associated with antiarrhythmic drugs (e.g. Class 1A: quinidine, disopyramide, and procainamide) by means of their QT-prolonging mechanism of action. More recently, this arrhythmia has been recognized with several pharmacological drug classes.[1,2] TdP has in part contributed to the recent market withdrawal of three agents (terfenadine, 1997; astemizole 1999; and cisapride 2000). Additional factors modulating cardiac repolarization (and therefore predisposing to QT prolongation) include: female gender, cardiac hypertrophy and heart failure (and thus age), hypokalemia, and potentially genetic factors (e.g. propensity to abnormal QT prolongation).[1]

Within the context of an ODE 4, QT-Working group, an Office of Postmarketing Drug Risk Assessment (OPDRA) consult was generated to evaluate postmarketing data relevant to TdP for an upcoming FDA Advisory Committee regarding telithromycin (Ketek®), NDA 21-144. Telithromycin is the first antibiotic within a new class of drugs (ketolides) pharmacologically related to the macrolides.[3,4] Macrolide antibiotics, specifically clarithromycin and erythromycin, have been associated with TdP via two mechanisms: 1. direct QT interval prolongation; and 2. indirect QT prolongation by inhibition of hepatic metabolism of other drugs causing QT prolongation (pharmacokinetic drug interaction).[5]

This document addresses the consult objective: analyses of postmarketing data to produce descriptive and quantitative data regarding TdP potential in macrolide antibiotics as it may relate to telithromycin, a new, pharmacologically similar drug.

METHODOLOGY

The FDA Adverse Events Reports System (AERS) and IMS HEALTH Audits™ were queried for TdP reports and drug utilization, respectively. Since telithromycin (a ketolide antibiotic) shares pharmacodynamic properties of the macrolide antibiotics, four macrolide antibiotics were considered: azithromycin, clarithromycin, dirithromycin, and erythromycin. In effort to systematically extract pharmacoepidemiological data in the AERS reports, a database was created for the storage and analyses of relevant variables and data.

The FDA AERS database was queried using two search criteria since TdP was not coded in the system prior to 1995. For the query after 1995, the following search criteria were used: respective macrolide trade name (T), active ingredient (A), and verbatim (V) for the drug of interest and "Torsade de Pointes" as a preferred term (PT). Prior to 1995, "Ventricular Tachycardia" was used as the preferred term, and the text was specifically evaluated for documentation of "Torsade de Pointes." All reports were manually reviewed. Duplicate reports for the same case, reports without Torsade de Pointes identified in the text (prior to 1995), and/or reports that were miscoded were deleted.

Information extracted from the AERS reports included demographic/anthropometric data, drug characteristics (e.g. dose, route), concomitant drugs and disease states, and

event characteristics (e.g. baseline QT, event QT, days to event). Particular attention was given to two, non-mutually exclusive subclasses of concomitant drugs: QT- prolonging drugs and contraindicated drugs/drug interactions (Appendix A.) For event characteristics, baseline QT was defined as a QT interval reported antecedent to the suspected drug exposure or event. Additionally, a QT reported after the event was considered "baseline" if the pre-defined, following criteria were met: it was clearly identified in the text as "baseline" or the equivalent, its report followed the discontinuation of the suspect drug(s) in a clinically acceptable time frame, and/or no intervention was employed that could prolong the QT (e.g. pacemaker, pharmacological therapy).

Two OPDRA staff extracted data. Two subjective criteria (Report Quality and Suspected Causality) for each AERS report were prospectively defined and considered for each AERS report (Appendix B). Data was extracted and stored in an Access Database. Approximately 20% of the data was confirmed by manual comparison of the AERS report – database printout. All data was evaluated for duplicates prior to analyses. Routine statistical procedures were employed using PC SAS (v. 6.12, The SAS Institute, Cary, NC).

IMS HEALTH Audits™ was queried for estimation of macrolide drug utilization. The National Prescription Audit (NPA) database was used to estimate domestic, outpatient prescriptions for macrolide use since telithromycin is available in an oral formulation only. The time window searched was from 1993 (or month the drug was available) until June 2000. The number of total dispensed prescriptions was used to approximate the extent of use in estimating crude reporting rates.

The number of domestic, oral formulation reports was calculated in the estimation of *relative* TdP reporting rates among the macrolide antibiotics,. A crude estimate of the reporting rate was calculated by division of the number of domestic, oral formulation TdP reports by the number of total prescriptions dispensed for each macrolide. Since the objective of this analysis was to give a relative estimate of reported TdP cases and characteristics among the macrolide antibiotics, an additional step was taken. Since azithromycin has not been shown to prolong the QT interval or inhibit hepatic metabolism, the macrolide reporting rate ratios were compared using azithromycin as the reference. That is, the reporting rates of clarithromycin, dirithromycin, or erythromycin were compared to azithromycin based upon TdP reports and IMS utilization.

Finally, the adverse events for azithromycin, clarithromycin, dirithromycin, erythromycin, and quinidine (positive reference) were also analyzed using a Bayesian data mining method adapted for large frequency tables with many small or empty cells (i.e., values of 0 and 1), such as drug/event combinations in a large spontaneous reporting system.[6] This method compares the observed frequency of reports for a specific drug/event combination to the expected frequency of reports for that adverse event in the entire AERS database (i.e., in association with any drug). For example, the frequency of observed reports of abdominal pain associated with bethanecol would be compared to the frequency of all reports of abdominal pain associated with any drug in the database. An Empirical Bayesian (EB) score is then calculated to represent an adjusted ratio between the observed frequency of the drug/event combination and the expected frequency in the AERS database. EB scores of ≥ 2 are generally considered to represent "interestingly large" counts of drug/events that are worthy of investigation.

RESULTS

FDA Spontaneous (AERS) Reports

As a result of the AERS query, 243 reports from 1987 through June, 2000 were reviewed. One hundred and fifty-two reports were included in the analysis (Table 1). Forty-one duplicate cases (including multiple follow-up, greater than 1 manufacturer reporting) were excluded and 38 reports were deleted for other established criteria (e.g. miscoded or Torsade de Pointes not in text). The overall quality of the reports was considered of average or greater quality (55%). Causal association was deemed likely/strongly suspect in nearly half (44%) of the reports.

Table 2 provides an overview of the 152 AERS reports. Based upon reports providing demographic data, the cases represented an older (60 years, N=141), female (72%, N=143) population consistent with the demographics and risks for TdP. Erythromycin accounted for the majority (54%) of reports followed by clarithromycin (34%). Eighteen (12%) of the macrolide-associated TdP reports included azithromycin as the suspect drug, although azithromycin is not labeled to cause QT-prolongation or inhibit hepatic metabolism. Causal association deemed likely/strongly suspect was lowest among azithromycin reports (33%).

QT event data was available in a limited number of reports (37 baseline, 55 event, and 35 with both baseline and event). 58% of the QT reports were identified as QTc (corrected for heart rate). The mean baseline QT interval (437 msec) was within acceptable limits based upon the QT interval used for exclusion (> 460msec) criteria in a clinical trial (Diamond Study) of dofetilide, an antiarrhythmic known to prolong the QT interval.[5] The mean event QT was markedly greater (592 msec). The mean duration between the initiation of the primary suspect drug and actual TdP date was 7 days (N=98), a potentially biased statistic due to two significant outlier reports (days to event = 120 and 140). If omitting these reports, the mean days-to-event statistic is notably shorter, 4 days.

In attempt to explore the relationship between the baseline and event QT intervals, two procedures were performed. An Event versus Baseline QT scatterplot, although limited by a small number of data points, suggests a positive, linear relationship (Figure 1). The corresponding Pearson Correlation Coefficient (r=0.51) indicates moderate, positive correlation. Figure 2 displays the univariate linear regression (Event QT = dependent variable, and Baseline QT = independent variable) model resulting in a significant, positive Baseline QT parameter estimate (0.81, p=0.002) although the coefficient of determination was small ($R^2 = 0.26$). A quadratic term introduced to the model was nonsignificant (p= 0.19). These data suggest a continuous increase in the event QT (and risk for TdP) with increasing baseline QT interval without a threshold or plateau.

Concomitant disease states or risks were common in the AERS reports (Table 2). While reports of renal and hepatic dysfunction were rare ($\leq$ 11%), at least one cardiac disease state was recorded in 43% of the AERS reports. Cardiomyopathy (24%) was the most common reported cardiac disease (Table 3). In addition to cardiac disease states, we also extracted data (arrhythmia, clinical event) reported in addition to TdP. QT prolongation, ventricular tachycardia, and syncope were reported in 30-40% of all reports

(Table 4). Last, hypokalemia or hypomagnesemia, two risk factors, were recorded in 18% of the reports.

A significant proportion of the reports listed multiple concomitant medications, (mean = 4 drugs, SD = 3, range = 0 – 15). Greater than half of the reports (52%) included concomitant drugs or drug classes known to prolong the QT interval. Approximately 1/3 of the reports included at least one of three contraindicated suspect drugs (astemizole, cisapride, and terfenadine) known to have pharmacokinetic drug interactions with erythromycin and/or clarithromycin (Figure 3a). Of these drug interactions, cisapride accounted for the largest proportion (Figure 3b). These three drugs have been withdrawn from the US market.

National Prescription Audit (NPA) IMS Drug Utilization

Over [redacted] macrolide antibiotic prescriptions have been dispensed in the retail pharmacy setting since 1993. Azithromycin accounts for greater than [redacted] of all macrolide prescriptions (Table 5). The graphical display of this data demonstrates a positive trajectory for azithromycin while clarithromycin use appears to reach a plateau. Erythromycin use continues to decline (Figure 4). Dirithromycin has taken no significant proportion of the market ([redacted] prescriptions annually).

Estimation of Risks Regarding Macrolide Antibiotics and Torsade de Pointes

The AERS and IMS utilization databases do not permit calculation of the incidence of TdP among users of macrolides because of the inherent spontaneous reporting system limitations and the utilization information on prescriptions dispensed rather than on patients treated. However, the relative TdP reporting frequency among the macrolide antibiotics given their different drug utilization patterns may be calculated and compared (Table 6). The reporting rate ratios for clarithromycin and erythromycin were 3.9 and 1.3 times, respectively, greater than azithromycin. There were no dirithromycin TdP reports.

As stated above, the absolute risk of a drug to produce TdP can not be quantified with this data. However, given the sum total of macrolide reports, one may consider the proportion of suspect drugs currently on the market. Fifty-one of the 152 reports (34%) had contraindicated drugs recently removed from the marketed listed as concomitant drugs. Therefore, substantial *potential* risks have been removed. However, a substantial proportion (22%) of the cases listed concomitant QT-prolonging drugs. It is this proportion in addition to the inherent QT prolonging qualities of a new drug that must be given attention.

Finally, analysis of the annual TdP report number for all macrolide antibiotics for the last 13 years demonstrates a spike around 1995 followed by a steady decline (Figure 5). Potential reasons for the spike include reporting bias following literature reports of TdP as well as the temporal association of TdP coding in the MedWatch system. Additionally, a possibility for the overall low number of reports is the fact TdP is a labeled event. It is possible the Agency receives fewer reports for *labeled* events. Due to these and other limitations, little definitive conclusion may be drawn. However, one substantive interpretation is the number of reports appears to be decreasing and more certainly does not appear to be increasing in frequency.

Data Mining for Torsade de Pointes Signals

The macrolide antibiotics were considered as suspect drug and Torsade de Pointes as the serious event in data mining. All three macrolides generated signals for TdP (dirithromycin has no reports). Erythromycin had the strongest signal (8 and $\leq$ 16). This estimate may be inflated due to the inclusion of IV formulations. Both azithromycin and clarithromycin generated relatively weak signals (2 and $\leq$ 4). As a comparator, quinidine generated a strong signal (8 and $\leq$ 16). These findings suggest as a class, macrolide antibiotics generate data mining signals ranging from one-forth to equal strength as an antiarrhythmic agent known capable of inducing TdP via mechanism of action.

DISCUSSION

We systematically reviewed macrolide-associated Torsade de Pointes spontaneous reports in effort to provide a descriptive and limited quantitative summary of this complex, potentially fatal adverse event. We found the reports representative of an older, female population. Polypharmacy, comorbid diseases, and electrolyte abnormalities were prevalent and appear to be tangible risks. While a limited number of Torsade de Pointes reports included both "baseline" and "event" QT values, there was a moderate correlation and linear appearance between the two variables suggesting a continuous increase in the potential for TdP as the baseline QT interval increases.

This is the first extensive analysis of reported Torsade de Pointes and macrolide antibiotics. Strengths of the analysis include the creation of a database for the systematic entry of pharmacoepidemiological data. Two individuals (DS, SS) reviewed and extracted all data using standard variable extraction guides and prospectively defined criteria. While other databases (e.g. Georgetown University) are being developed or ongoing, the FDA Adverse Events Reporting System arguably contains the greatest amount of postmarketing data regarding Torsade de Pointes at this time in the United States.

Limitations of the analysis are germane to the FDA Adverse Event Reporting System.[7] Biases in reporting rates may be bi-directional. For example, a publication bias may be responsible for the transient increase in reports around 1995. Under reporting has been a longstanding limitation. It is estimated that the FDA receives anywhere from < 1-10% of adverse drug reactions depending upon the severity.[7] Limitations in the completeness of data contained on AERS reports can not be overcome *post-hoc*. However, it is worth noting in attempt to gather as much information as possible, all reports were analyzed (including multiple reports for the same case). Finally, uncertainty in the diagnoses of Torsade de Pointes is well recognized. In effort to overcome coding misclassification, all reports were validated to have "Torsade de Pointes" specifically within the text. However, it is possible other adverse events (e.g. syncope, sudden death) included Torsade de Pointes, but the arrhythmia was not observed and reported.

We used data mining to evaluate the relative signals of the macrolide antibiotics for TdP while considering quinidine as a positive reference. The strength of DM is that it can be used as an objective screening tool to assist in the initial separation of potential safety signals from random reporting patterns, particularly when small numbers of reports are involved. Limitations of DM include that it does not have the capability to distinguish between labeled and unlabeled events, cannot adjust for the severity of the

event and is not a substitute for careful clinical case review. Additionally, since the erythromycin signal includes IV formulations, it is probably reasonable to consider all oral macrolide antibiotics to generate a signal for TdP 2-4 fold less than quinidine.

Since postmarketing data is obviously unavailable for telithromycin, direct comparison can not be made. Generalizations based upon this analysis **must** be taken with extreme caution and in the context of the data available. It is generally accepted knowledge in the scientific community with regard to the Evidence Based Medicine hierarchy that the randomized controlled trial is superior and followed by cohort analyses. However, when these are unavailable, we must rely on the best available evidence. This has been a systematic attempt to analyze in depth best available data. Given that, loose generalizations may be considered.

Telithromycin is structurally similar to macrolide antibiotics. Telithromycin is metabolized by the cytochrome P450 3A4 system and "there is most likely a drug effect on cardiac repolarization manifested by a concentration related lengthening of the QTc interval." [8] Given these two properties, it is not unreasonable to anticipate QT prolongation and potentially Torsade de Pointes in postmarketing surveillance. It is worthy to reiterate that no incidence calculations are permissible with the data contained within this analysis. However, when considering only domestic, oral-formulation reports and accounting for national drug utilization patterns, clarithromycin had the greatest crude reporting rate estimate. To the extent telithromycin is similar to clarithromycin (hepatic metabolism, QT prolongation), this data suggests the potential for QT-prolongation, and clinical postmarketing adverse events.

CONCLUSIONS

Torsade de Pointes is a rare, potentially fatal cardiac arrhythmia identified with macrolide antibiotics and well represented in postmarketing spontaneous report data. Concomitant risks (e.g. drug, disease, and electrolyte) represent confounding factors in the postmarketing milieu not always foreseeable in the confines of premarketing trials. While risks such as drug interactions (astemizole, cisapride, and terfenadine) have been recognized and addressed by the agency, confounding risks remain. To the extent telithromycin shares hepatic inhibition and inherent QT prolongation as clarithromycin, it is reasonable to expect QT prolongation and potentially Torsade de Pointes in postmarketing surveillance. This potential must be clearly addressed in the telithromycin label and consideration of [redacted] should be undertaken.

CONSULTATION SIGNATURE PAGE

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February 20, 2001

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February 15, 2001

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8) Gordon M. Division of CardioRenal Drug Products Consultation. 2 October 2000.

Table 1. FDA Adverse Event Report System (AERS) Query: Macrolide Antibiotic and Torsade de Pointes (1987 – June, 2000)

Macrolide	AERS Reports		Duplicates[§]	Deletions[§]	Analyzed
	After 1995	Before 1995*			
Azithromycin	23	3	3	1	18
Clarithromycin	57	21	16	9	52
Dirithromycin	0	0	0	0	0
Erythromycin	85	54	22	28	81
Total	165	78	41	38	**152**

* Ventricular Tachycardia was searched for dates prior to 1995. Reports without "Torsade de Pointes" in text were deleted.

§ Duplicates include multiple reports for the same case. Deletions and duplicates are not mutually exclusive. One case may have had several reports, one of which would be deleted for miscoding.

Table 2: Summary of Macrolide-Associated Torsade de Pointes AERS Reports (N=152)

	Data (N)[¶]	Mean (+/- SD) or Frequency [%]	
Report Characteristic			
Quality (average or greater)		83 [55%]	
Causality (highly/strongly suspect)		67 [44%]	
Foreign Origin		34 [22%]	
Duplicate Reports		41 [27%]	
Demographic/Anthropometric			
Age (years)	141	60 (+/- 22)	
Gender (female)	143	103 [72%]	
Race (other than Caucasian)	22	7 [32%]	
Weight (lbs.)	41	152 (+/-32)	
Macrolide Reports {# IV}			
Azithromycin		18 [12%]	{4}
Clarithromycin		52 [34%]	
Dirithromycin		0	
Erythromycin		82 [54%]	{37}
Event Characteristics			
Baseline QT (msec)	37	437 (+/-48)	
Event QT (msec)	55	592 (+/-80)	
Days to Event[§]	98	7 (+/-18)	
QTc reported[•]		32 [58%]	
Concomitant Drugs[ϕ]			
Number		4 (+/- 3)	
QT Prolonging[Ψ]		79 [52%]	
Drug Interaction[Ω]		53 [35%]	
Concomitant Risks[ϕ]			
Cardiac Disease		65 [43%]	
Renal Disease		16 [11%]	
Hepatic Disease		9 [6%]	
Laboratory Abnormalities		27 [18%]	
Reports of Death		13 [9%]	

¶ Only partial AERS reports (N) had complete data (demographic, event characteristics e.g.)

• QTc provided in 32 reports; QT or unspecified in remaining 23

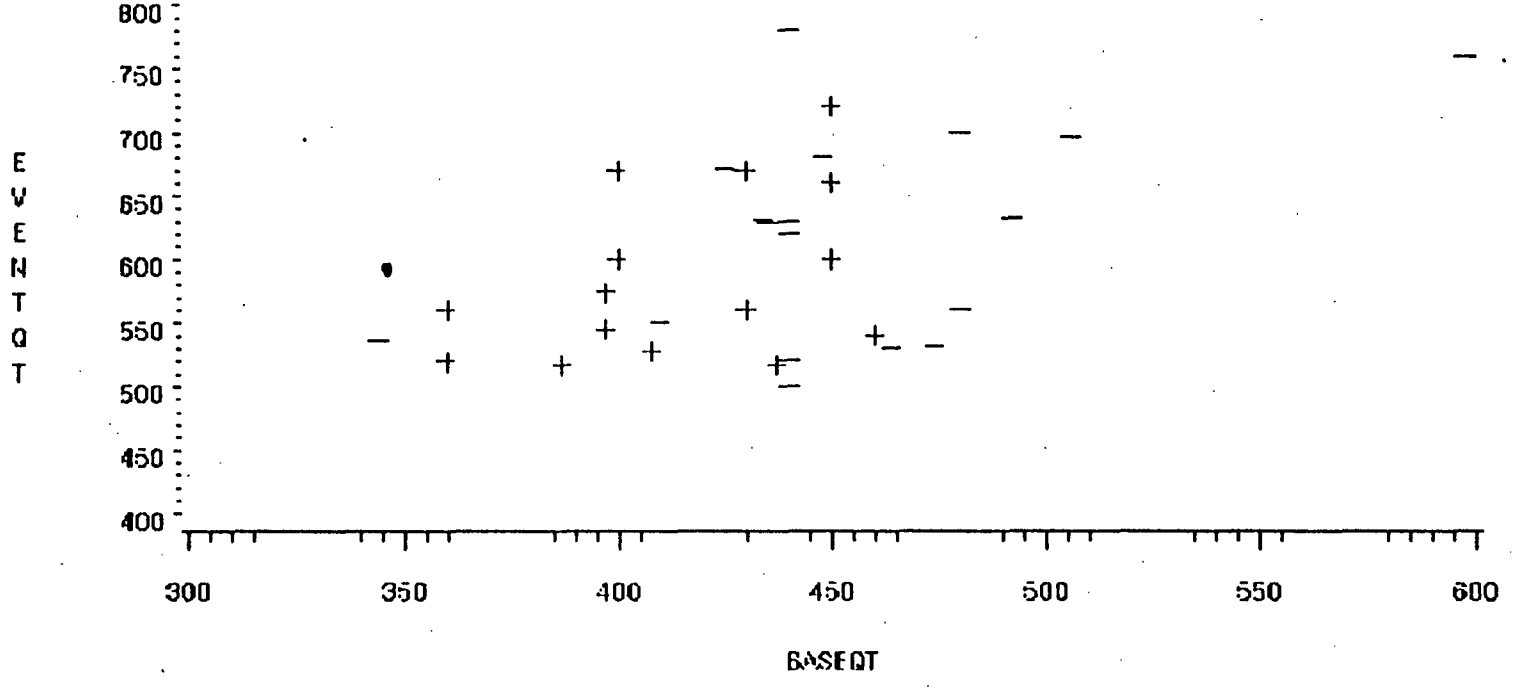
§ After 2 outliers excluded (120, 140 days), mean = 4 days (+/- 3)

ϕ Frequency of concomitant drugs and risks based upon mention/occurrence in AERS reports

Ψ QT Prolonging drugs: Antiarrhythmics, Tricyclic Antidepressants, Neuroleptics, Antifungals (Ketoconazole), Non-sedating Antihistamines, Cisapride

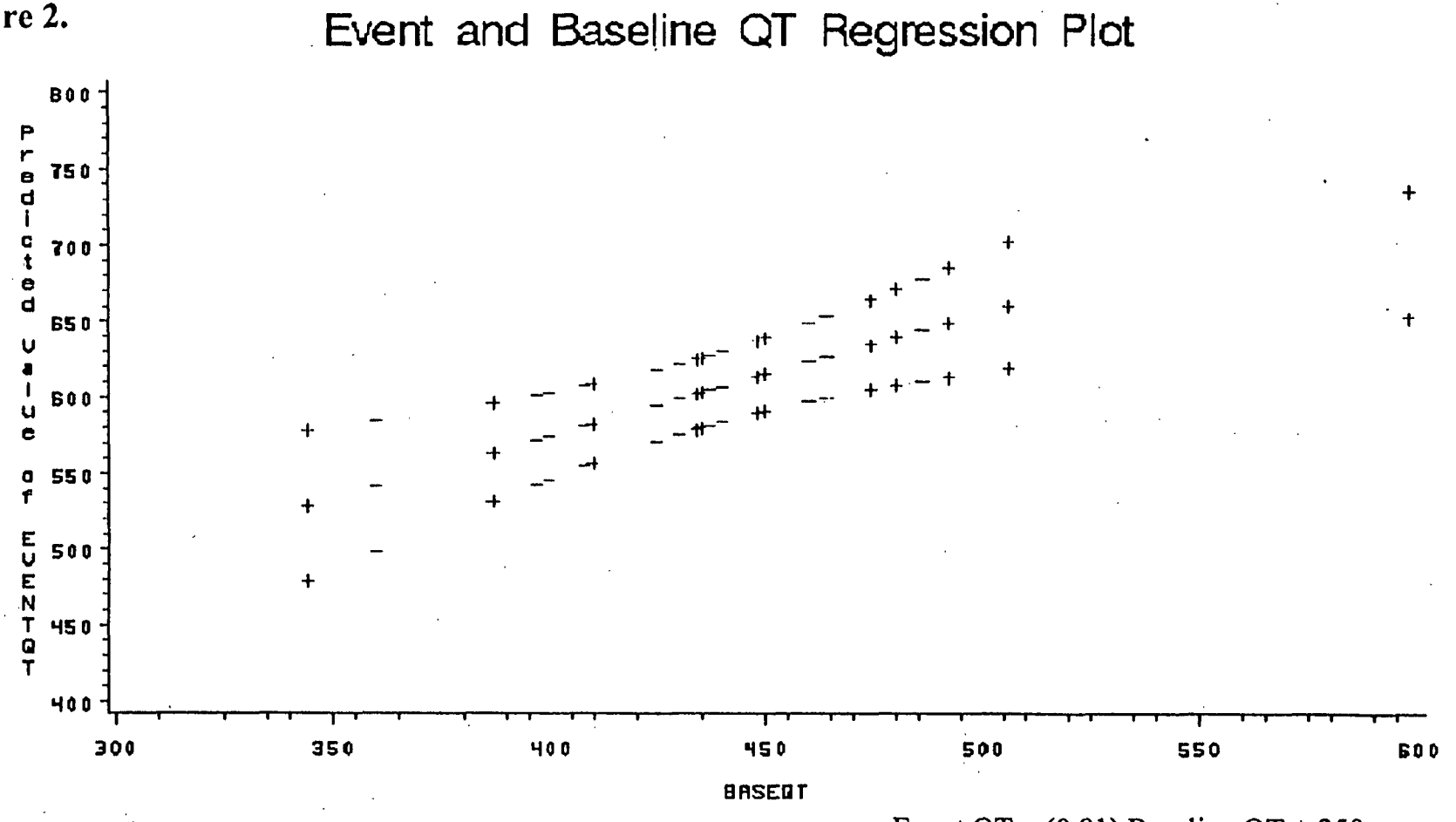
Ω Drug Interaction: Macrolide + Astemizole, Cisapride, Pimozide, or Terfenadine

Figure 1. Event vs. Baseline QT Scatterplot



Pearson Correlation Coefficient = 0.51
N=35

Figure 2.



Event QT = (0.81) Baseline QT + 250
$R^2 = 0.26$
$p = 0.002$

Table 3. Classification of Cardiac Disease in 152 Torsade de Pointes AERS Reports

Cardiac Disease*	N [%]
Cardiomyopathy/Congestive Heart Failure	36 [24%]
Coronary Artery Disease	25 [17%]
Valve Disease	14 [9%]
Atrial Fibrillation	12 [8%]
Pacemaker/Defibrillator	10 [7%]
Other*	31 [20%]

* Groups are not mutually exclusive. All but other were considered in reporting frequency of cardiac disease.

** Includes rhythm disturbances (bradycardia, atrio-ventricular block e.g.), may be falsely elevated by presence of hypertension.

Table 4. Simultaneous Reports of Cardiac Arrhythmias / Events in 152 Torsade de Pointes AERS Reports

Cardiac Terminology	N [%]
QT Prolongation	60 [40%]
Ventricular Tachycardia	54 [36%]
Syncope	46 [30%]
Cardiopulmonary Arrest/Sudden Death	29 [19%]
Ventricular Fibrillation	20 [13%]
Bradycardia	5 [3%]
Tachycardia	2 [1%]

Figure 3a. **Macrolide Antibiotics and Torsade de Pointes (N=152) - Concomitant Drugs**

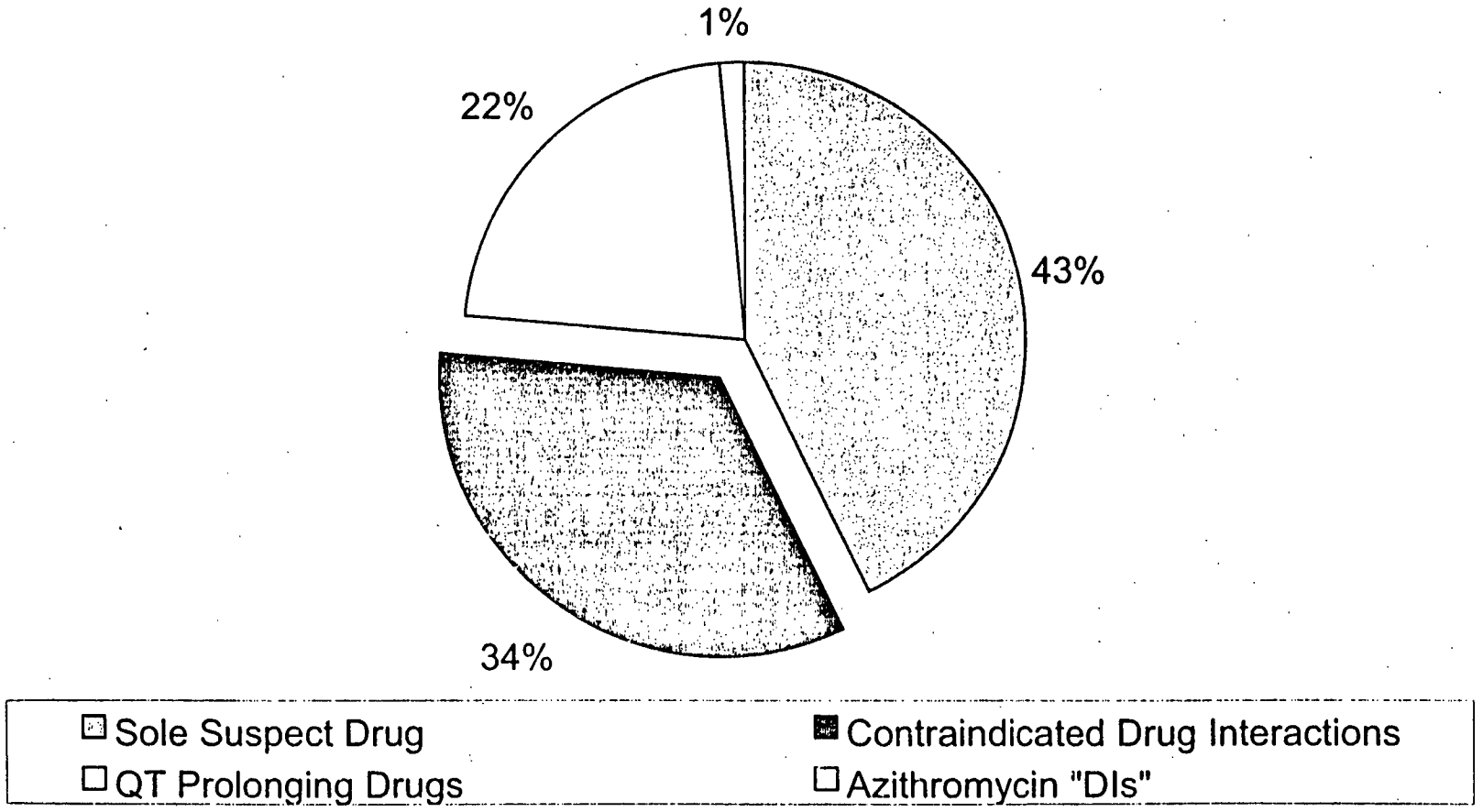


Figure 3b. **Contraindicated Drug Interactions (N=51) in Clarithromycin and Erythromycin Torsade de Pointes Reports**

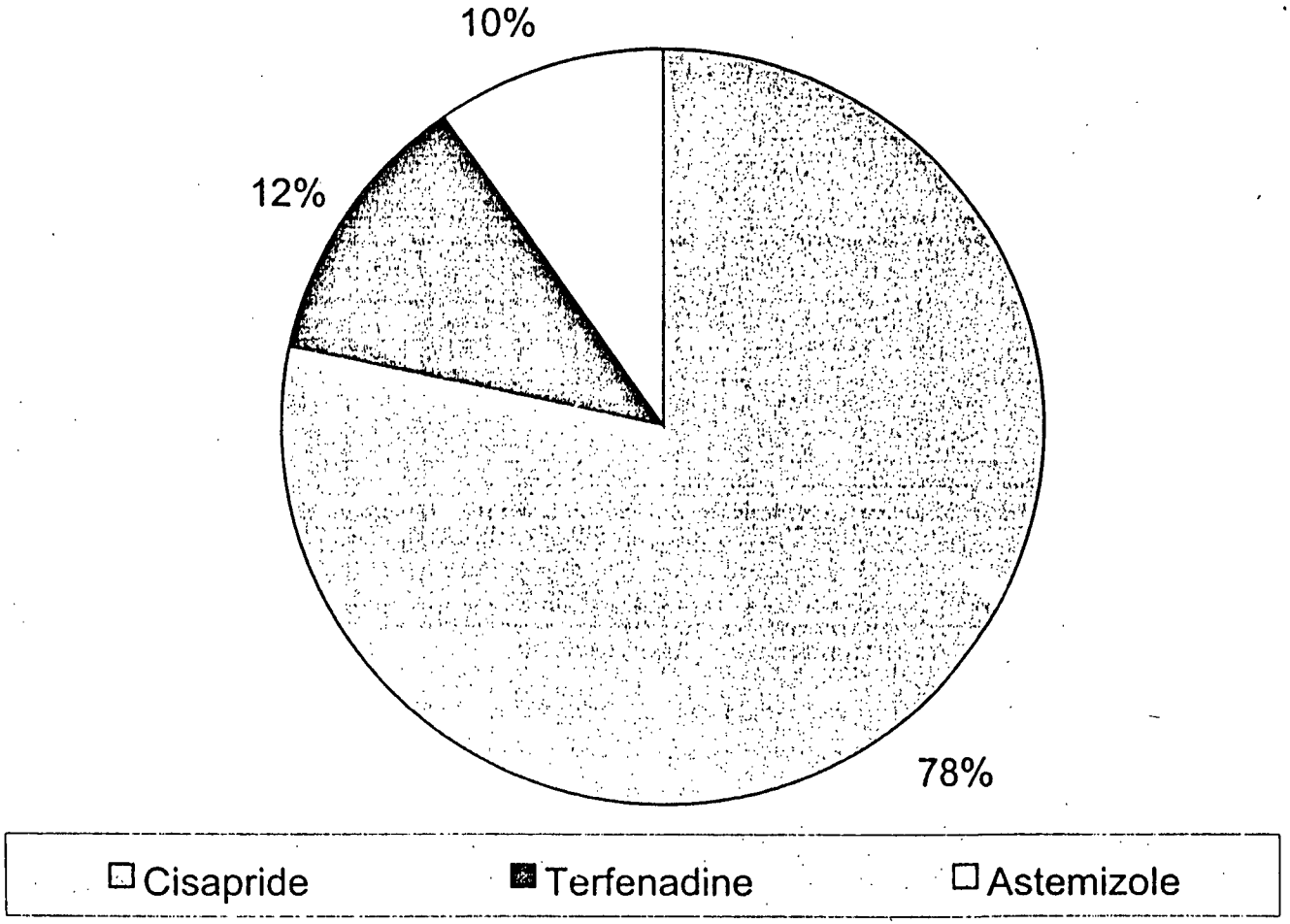


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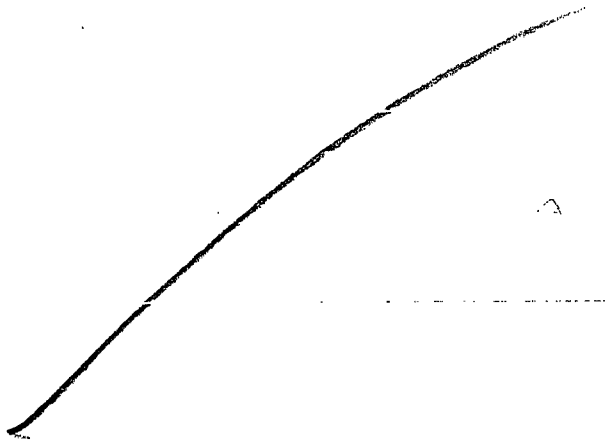
Table 6. Macrolide Antibiotics: Adjusted Torsade de Pointes Reports and Drug Utilization Data

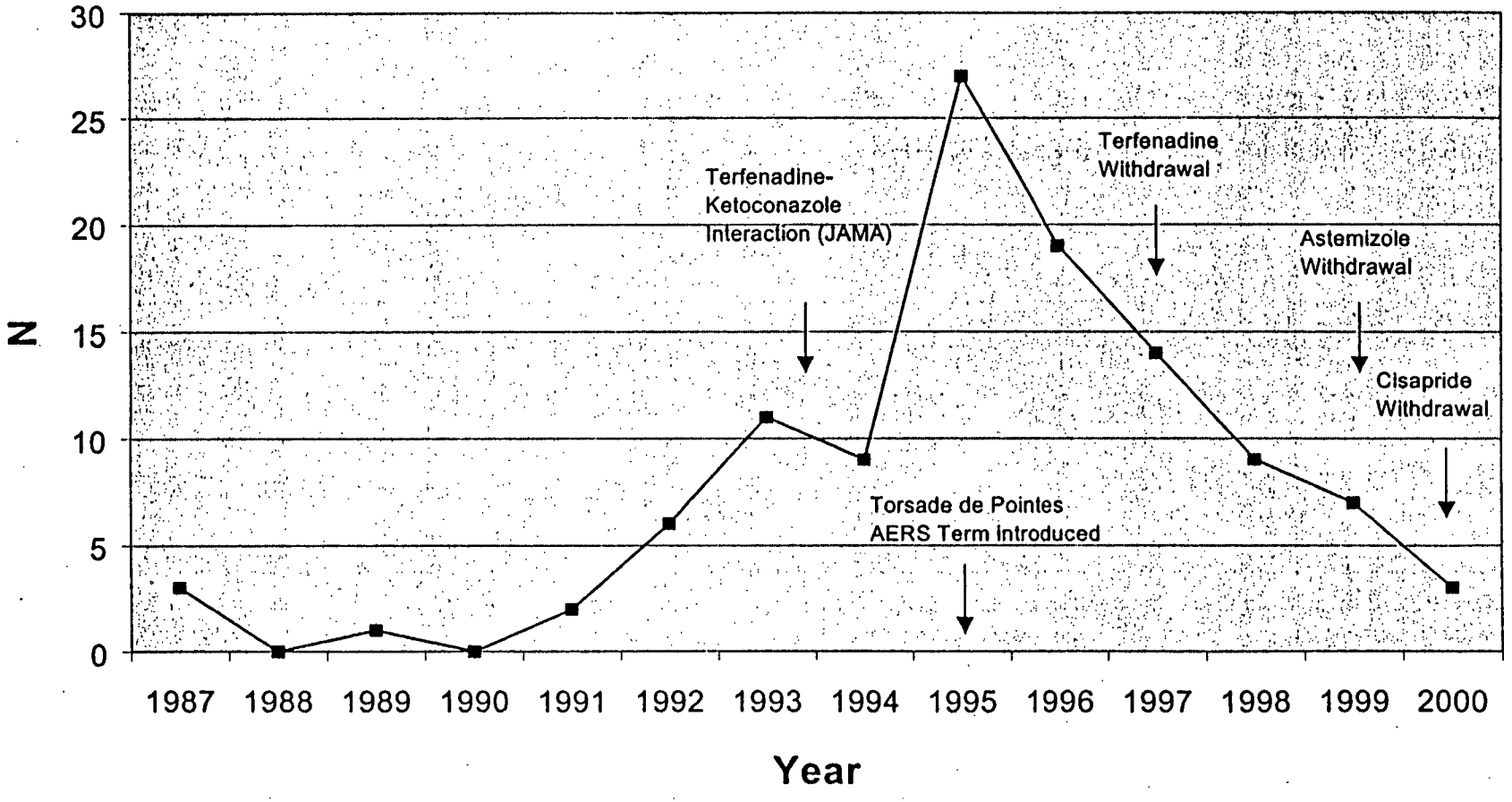
Macrolide	Reports (N)	Utilization	Crude Reporting Ratio* (reports/utilization)	Relative Ratio
Azithromycin	10			
Clarithromycin	31			
Dirithromycin	0			
Erythromycin	17			



* Defined as the number of domestic, oral-formulation reports of Torsade de Pointes given the 1993 –June 2000 US retail drug utilization data

Figure 5.

Historical Markers & Macrolide-Associated Torsades de Pointes



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