Division of Anti-Infective and Ophthalmology Products (DAIOP)

Briefing Document

Joint Meeting of the Anti-Infective Drug Advisory Committee

and

Drug Safety and Risk Management Advisory Committee

December 14-15, 2006

NDA 21-144

Ketek® (telithromycin)

DAIOP Briefing Document
Joint Meeting of the Anti-Infective Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee: December 14-15, 2006
Ketek (telithromycin)

I. INTRODUCTION.....4
II. APPROVAL HISTORY FOR KETEK.....6
III. SUMMARY OF OVERALL SAFETY.....9
A. Hepatic effects.....10
B. Visual effects.....11
C. QT effects, drug-drug interactions, and special populations.....12
D. Exacerbation of Myasthenia Gravis.....13
IV. SUMMARY OF OVERALL EFFICACY.....14
A. Acute Bacterial Exacerbation of Chronic Bronchitis.....14
B. Acute Bacterial Sinusitis.....16
C. Community-Acquired Pneumonia.....19
V. SUMMARY OF AGENCY CONCLUSIONS AND ACTION.....26

VI. POST-MARKETING INFORMATION FOR KETEK.....27
VII. APPENDICES.....28

LIST OF ABBREVIATIONS

ABECB – Acute Bacterial Exacerbation of Chronic Bronchitis

ABS – Acute Bacterial Sinusitis

CAP – Community-Acquired Pneumonia

COPD – Chronic Obstructive Pulmonary Disease

ERSP – Erythromycin-Resistant *Streptococcus pneumoniae*

HED – Human Equivalent Dose

MDRSP – Multi-Drug Resistant *Streptococcus pneumoniae*

MITT – Modified Intent-to-Treat Population

NDA – New Drug Application

PPb – Bacteriological Per Protocol Study Population

PPc – Clinical Per Protocol Study Population

PRSP – Penicillin-Resistant *Streptococcus pneumoniae*

TOC – Test-of-Cure Visit

TP – Tonsillopharyngitis

I. INTRODUCTION

Ketek® (telithromycin) is an oral ketolide antibiotic, marketed in the United States by Sanofi-Aventis as 300 mg and 400 mg tablets. Ketolide antibiotics are structurally related to macrolide antibiotics (erythromycin, clarithromycin, and azithromycin), and have in vitro activity against a similar range of respiratory pathogens (*Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae*). Telithromycin retains activity against strains of *Streptococcus pneumoniae* that are resistant to other macrolides. (See Appendix A for detailed Microbiology information.) Currently, telithromycin is the only ketolide antibiotic approved for marketing in the United States.

Ketek® (telithromycin) was approved on April 1, 2004 for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years old and above:

- **Acute bacterial exacerbation of chronic bronchitis** due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.
- **Acute bacterial sinusitis** due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.
- **Community-acquired pneumonia** (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.

Consistent with other contemporary antibacterial development programs seeking similar claims, the above indications were approved based upon the results from clinical trials designed to show non-inferiority. While studies of this design have been the standard for determining the safety and efficacy of approved antibacterial agents, recent discussions have raised significant questions about the interpretability of a finding of non-inferiority in some infectious diseases, notably less serious, typically self-limited infections such as acute bacterial sinusitis and less severe acute bacterial exacerbation of chronic bronchitis.

The section of this document titled "***APPROVAL HISTORY FOR KETEK***" provides a summary of the complexities of the New Drug Application (NDA) for Ketek, and focuses on the safety and efficacy information relevant to the three approved indications. The data that supported the approval of the Ketek NDA (NDA 21-144) in April 2004, including controlled and uncontrolled studies in the NDA and information from spontaneous adverse event reports from almost 4 million prescriptions in Europe and Latin America.

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

Since approval in the U.S. in April, 2004, the Division of Anti-Infectives has continued to review post-marketing adverse event reports for Ketek® and to consult both the Office of Surveillance and Epidemiology and Office of Biometrics to understand the spontaneous adverse event reports, their context in the number of prescriptions written, and how to use such data as the basis for further regulatory action (e.g., posting a Public Health Advisory, changing product labeling). The safety concerns discussed in the two previous Anti-Infective Drugs Advisory Committee (AIDAC) meetings on Ketek (April 2001 and January 2003) have continued to be the main areas of focus regarding safety.

Following the online publication of an article in the Annals of Internal Medicine of three patients who experienced serious liver toxicity following administration of Ketek, FDA posted a Public Health Advisory on January 20, 2006 providing interim recommendations to health care providers. In June 2006, a follow-up MedWatch Alert was posted about rare cases of serious liver injury and liver failure following administration of Ketek, and the Ketek product labeling was revised to include additional Warnings regarding hepatotoxicity and also exacerbations of myasthenia gravis. In addition to reviewing information on hepatic toxicity, additional information on other labeled adverse events for Ketek (exacerbation of myasthenia gravis, effects on vision, and syncope) has also been reviewed. This information is discussed in "***POST-MARKETING INFORMATION FOR KETEK***" section of this document.

In the context of this growing body of safety-related information, usage data of

approximately 27 million exposures worldwide (over 5 million in the US), and recent labeling changes, the FDA is reviewing the overall risk/benefit assessment for Ketek. This joint meeting of the AIDAC and Drug Safety and Risk Management Advisory Committee (DSaRM) is being convened to obtain external advice on the overall risk/benefit considerations for Ketek and possible next regulatory steps. The points that the Committee will be asked to discuss include:

- the risks and benefits for each of the approved indications for Ketek (community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), and acute bacterial exacerbation of chronic bronchitis (ABECB)), taking into consideration the current safety information (i.e., hepatic, visual, and neurologic adverse events);
- whether the overall risk/benefit profile supports continued marketing of Ketek for any of the approved indications (CAP, ABS, ABECB);
- if continued marketing is recommended, whether the product label adequately describes the adverse events (specifically including hepatic, visual, and neurologic adverse events) and whether additional communication strategies or other risk management programs should be implemented to ensure safe use of this drug;
- whether any additional studies are recommended to further elucidate the benefit/risk assessment of Ketek.

II. APPROVAL HISTORY FOR KETEK

The Division of Anti-Infective Drug Products/Office of Drug Evaluation 4 approved Ketek in April, 2004 for the treatment of adults with respiratory tract infections, including community-acquired pneumonia (of mild to moderate severity), acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis. The data included experience with 47 pneumonia patients with pneumococcal bacteremia. The approval included treatment of patients with pneumonia due to multi-drug resistant *Streptococcus pneumoniae*.

Ketek was submitted as an NDA in March, 2000 by Aventis Pharmaceuticals, Inc. The Agency concluded that while efficacy was generally demonstrated, significant safety concerns existed, and too few patients had infections with resistant bacteria to permit an overall risk-benefit assessment. Safety problems included potential liver toxicity, QT prolongation with potential cardiac arrhythmias, drug-drug interactions, and visual side effects. At an Advisory Committee meeting in April, 2001, AC members recommended approval for treatment of CAP, though they also recommended additional studies to delineate the drug's safety profile (prior to AECB or ABS approval) and to gain experience with patients with pneumonia due to drug-resistant *Streptococcus pneumoniae*. Aventis conducted these additional studies during 2001-2002, including a large controlled safety trial in a usual care setting in outpatients with respiratory tract infections (Study 3014). Review of Study 3014 was complicated by systematic failure of the clinical trial monitoring program to detect data integrity problems when they in fact existed, making it difficult to rely on this study to support a regulatory action. Internal FDA discussion at a Regulatory Briefing

concluded that if the results of Study 3014 could not be relied upon, analysis of ex-US post-marketing usage data and adverse event reports could serve as the additional safety information to augment the Agency's risk/benefit assessment. When Aventis resubmitted the NDA in October, 2003, our understanding of the overall risk/benefit profile of Ketek was enhanced by information from spontaneous adverse event reports for approximately 4 million prescriptions in Europe and Latin America.

Summary of Events

• In March, 2000, Aventis submitted the NDA for Ketek for treatment of respiratory tract infections in adults, seeking approval for four indications (community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and tonsillopharyngitis), including a claim for drug-resistant *Streptococcus pneumoniae.* Few data were submitted on patients with infections due to resistant bacteria.

• The Agency discussed the Ketek NDA at an April, 2001 Advisory Committee meeting, concluding that clinical trials revealed similar efficacy for Ketek and comparator antimicrobial drugs (except for tonsillopharyngitis, where substantial evidence of efficacy was not demonstrated). But safety concerns led Advisory members and the Agency to ask for additional safety and efficacy data. The Agency issued an approvable letter in June, 2001.

• Safety information in animals and man led to three main concerns: hepatic, cardiac (increased QT interval and drug-drug interactions), and visual side effects. In patients treated with Ketek, a cluster of liver enzyme elevations occurred in elderly patients, and a case of biopsy-confirmed eosinophilic hepatitis was consistent with a drug-induced liver injury.

• Aventis submitted additional efficacy and safety studies in July, 2002, including study 3014, a 24,000 patient usual care study in mild respiratory infections. As noted above, inspections of this study raised questions regarding trial monitoring to detect data integrity problems.

• On January 8, 2003, in the midst of ongoing inspections of Study 3014, a second public meeting of the Anti-Infective Drugs Advisory Committee was held to discuss the available information for Ketek. This included analyses of all phase 3 studies, in addition to the results of study 3014. The Committee voted in favor of approval for all three indications (CAP, ABS, ABECB), largely based on the results of the large safety study, though information from the phase 3 studies, additional mechanistic studies for visual adverse effects, studies evaluating QT effects, drug-drug interaction studies, and the foreign post-marketing experience were also taken into account. The Agency did not follow the Committee's advice at that time to approve Ketek, but instead issued a second approvable letter. The Agency requested information about trial monitoring for Study 3014 and

• In a closed session of the Anti-Infective Drugs Advisory Committee, held on March 6, 2003, the Division briefed the Committee on the Approvable action taken for Ketek and the need for additional information before the NDA could be further considered, noting problems that had been identified with data integrity in Study 3014.

• Aventis responded to the January, 2003 approvable letter, including an analysis of substantial post-marketing safety data for approximately 4 million prescriptions in Europe and South America.

Key Points in Approval History

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

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

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

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

Aventis submitted the requested studies in July, 2002. The Agency convened a second Advisory Committee meeting in January, 2003, and the Committee judged that safety and efficacy for the requested indications had been demonstrated, in large measure on the basis of study 3014. Presentation to the Advisory Committee, however, did not include a discussion of serious data integrity issues uncovered in this large usual care study by Agency inspections as they were ongoing at that time. Since description of the risks of telithromycin and assessment of its risk-

benefit profile (particularly with regard to hepatic and visual toxicities) rested heavily on this large safety study, the Agency issued a second approvable letter in order to better understand how study 3014 was conducted. The October, 2003 submission addressed issues of study 3014 conduct, and included as well post-marketing reports for spontaneous adverse events for approximately 4 million prescriptions for patients in foreign countries. Data integrity problems with some investigators in study 3014, coupled with systematic problems in trial monitoring, led to the conclusion that the study could not be relied upon to take a regulatory action. The Agency instead augmented its understanding of safety from clinical trials with post-marketing experience in 4 million European and Latin American patients to conclude there was substantial evidence of safety.

III. SUMMARY OF OVERALL SAFETY

The pharmacology/toxicology review of the telithromycin NDA submission found adverse effects on cardiac repolarization (effects on the QT interval), on the liver (including elevations in hepatic enzymes and histopathological changes) and kidney (histopathological changes, increased urinary N-acetyl-ß-glucosamidase), and on neurological function. Evidence of delayed cardiac repolarization elicited by telithromycin was seen in experiments *in vitro* in animal and human cells, and *in vivo* in animals. In the dog, telithromycin treatment resulted in a markedly increased heart rate and increased QT interval (27-30 milliseconds) in a 30-day study of daily oral administration at a dose of 90 mg/kg/day The HED is 45 mg/kg/day or approximately 2700 mg for a 60 kg patient; over 3 times the approved 800 mg daily dose. Effects on QT interval at lower doses may have been masked by the shortening of that interval that accompanies increases in heart rate. In a comparative study in dogs, clarithromycin and erythromycin each increased the QT interval by 17 milliseconds following a single dose; telithromycin increased the QT interval by 30 milliseconds after a single dose equivalent to a clinical dose of 450 mg to a 60 kg patient. Animal studies showed significant toxic effects of telithromycin on the liver in multiple species (mice, rats, dogs and monkeys), as manifested by increased liver-associated enzymes, increased total bilirubin, hepatic necrosis and associated inflammation, and phospholipidosis. In comparing these effects in animals given either telithromycin or clarithromycin, it was noted that the hepatotoxic effects appeared greater in animals administered telithromycin and that more species appeared to be sensitive to the hepatotoxic effects of telithromycin. Animal studies evaluating neurologic effects of telithromycin found increased locomotor activity and lowered threshold for pharmacologically-induced convulsions in rats at a high dose of telithromycin (300 mg/kg PO). The HED is 50 mg/kg, or 3000 mg for a 60 kg patient. In isolated phrenic nerve-diaphragm preparations from rats, exposed to two telithromycin concentrations, a concentration-dependent increase in the amplitude of contraction (75% at the highest concentration) followed by a progressive twitch inhibition (90% at the highest concentration) that lasted 150 minutes was observed, possibly reflecting effects on the neuromuscular junction.

Human exposure showed that telithromycin concentrations in plasma are highly variable (1.99 mg/L after a single dose, up to 9.9 mg/L after multiple doses). Telithromycin is a CYP 3A4 and 2D6 substrate, as well as a strong CYP3A4 inhibitor. It is primarily metabolized and eliminated by the liver. In subjects with liver impairment, the half-life of telithromycin significantly increased, as did the role of renal elimination.

Safety information in man led to the following main areas of concern: hepatic effects, visual complaints, potential CYP 3A4-mediated drug-drug interactions, and QT prolongation. Data collected from Phase 1-3 studies, and post-marketing exposures in approximately 4 million patients are summarized below for each area of concern.

A. Hepatic effects

In Phase 1 studies, 8 elderly subjects received a single 2 gram dose of telithromycin; 3 patients had elevated liver transaminase values (ALT and AST levels ranging from 100-300, ALT > AST). Phase 1 data showed no clear dose-response for hepatic adverse events. In Phase 3 studies, the observed rate of possibly drug-related serious hepatic adverse events in Phase 3 trials was 2/4472 (0.0004, 95% CI [0.0001, 0.0017]). Analyses of liver function tests from the comparative Phase 3 community-acquired pneumonia (CAP) studies in patients who were normal at baseline showed a greater proportion of patients with low to moderate elevations (1-2x ULN, 2-3x ULN, and 3-5x ULN) of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the telithromycin-treated patients than in comparator-treated patients. The AST and ALT elevations from patients in CAP studies were present during the On-Therapy and Post-Therapy visits. While infrequent, concomitant transaminase and total bilirubin elevations were only found in telithromycin-treated patients and were categorized as low level elevations between 1x and 2x the upper limit of normal (ULN). (See Appendix B for more detailed information on liver function test abnormalities in the phase 3 studies.)

Looking at all serious hepatic AE in the comparative studies, regardless of relationship to study drug, there were two serious hepatic AE reported in telithromycin-treated subjects and one serious hepatic AE reported in a comparator-treated patient. In the non-comparative studies, there was one additional serious hepatic AE in a telithromycin-treated patient. There were reasonable alternative explanations for one of the serious hepatic AE in the telithromycin-treated patients and for the only comparator treated patient with a serious hepatic AE. Two serious hepatic AE plausibly related to telithromycin were described as follows:

The first of these two events was a 76 year-old female with CAP and a history of hypercholesterolemia and hyperuricemia, maintained chronically on pravastatin 20 mg po qd and allopurinol 20 mg po qd. She experienced isolated asymptomatic elevations of alanine aminotransferase (ALT) (13x Upper Limit of Normal (ULN)) and aspartate aminotransferase (AST) (9x ULN) on Day 5 of therapy with telithromycin 800 mg po qd in the absence of an elevated total bilirubin. Telithromycin was discontinued on Day 6 of therapy. Her transaminase abnormalities had nearly resolved by Day 12. The other serious hepatic AE that the medical officer considered as quite possibly associated with telithromycin is described in the following 2 paragraphs.

A 53 year-old male with CAP from a study center in Finland was enrolled in the Study 3000, a non-comparative CAP study. At baseline his ALT was slightly elevated [ALT=81 U/L (normal range (NR) <49)] and his peripheral eosinophil count was 774 cells/10-6L (lab normal range not provided). He completed 10 days of telithromycin at 800 mg po qd. Four days after completing therapy, he developed a gastroenteritis-like illness similar to other members of his family, except that the subject's fever persisted. Ten days after completing therapy, he had laboratory studies drawn that demonstrated elevations of his ALT to 7x ULN and AST to 5x ULN with eosinophilia. His ALT increased to a peak of 31x ULN and his eosinophils peaked at 2856 cells/10^{-6} L. Serologic evaluations for hepatitis A, B, and C, were negative. Throughout the episode his total bilirubin was only mildly elevated (peak elevation 1.55x ULN). Other medications that the patient received around the time of this event included inhaled Atrovent,

salbutamol, and fluticasone, Nasonex spray (mometasone furoate), six 500-mg acetaminophen tablets over a one-week time period. His ALT elevation almost completely resolved in the absence of specific therapy by 6 weeks after initial detection of the hepatic event (AST levels were only infrequently monitored). As part of the evaluation of this episode of hepatitis, a liver biopsy was performed. Review of the liver biopsy at the Armed Forces Institute of Pathology found pathologic changes of centrilobular necrosis and eosinophilic infiltration, findings strongly suggestive of drug-induced liver disease.

Eight months later at a routine follow-up visit, the subject was noted to have an elevated ALT of 1331 U/L in the absence of eosinophilia. Prior to this second event there was no known antecedent exposure to a ketolide or macrolide class agent. Several weeks later he underwent a liver biopsy. Review of the patient's second liver biopsy at the Armed Forces Institute of Pathology found pathologic changes of chronic hepatitis with marked activity and extensive bridging fibrosis. These findings of chronic hepatitis were probably autoimmune.

The occurrence of what appeared to be a significant drug-related hepatic AE in the NDA database was of particular concern.

As of October, 2003, with approximately 4 million prescriptions written in Europe and Latin America, there were 90 reported telithromycin-associated hepatic adverse events reported by 43 different patients. (See Appendix C Foreign Post-Marketing Safety for details of these cases.) As is usually the case with spontaneous post-marketing reports, the majority of these lacked sufficient detail to assess causality or liver injury pattern. For those reports which did contain sufficient data, a cholestatic pattern of injury was most common. The pattern resembled a hepatocanalicular injury, well described in patients treated with erythromycins. There were less common reports of cytolytic injury. One death was reported due to a hepatic adverse reaction. This complex patient was felt to have had acute hepatitis A, possible Q fever, and high dose acetaminophen consumption. Although it is difficult to determine accurate incidence rates of adverse events based on post-marketing data, the number and severity of the telithromycin-related reports appear similar to erythromycins. As summarized in comments at the January, 2003 Anti-Infective Advisory Committee, telithromycin is clearly hepatotoxic, but the data collected at that point suggested that it is not significantly more hepatotoxic than other marketed antibiotics, and relative differences in toxicity between telithromycin and macrolides may only become evident during further post-marketing surveillance.

B. Visual effects

In studies of healthy volunteers conducted to understand the mechanism of visual effects, patients under 40 years of age received a single 2400 mg dose of telithromycin. (See Appendix D for a summary of the visual effect studies.) The incidence of blurred vision ranged from 27% to 83%. In older patients given 2400 mg, the incidence of blurred vision ranged from 0% to 33%. Blurry vision developed 1 to 3 hours after dosing and lasted up to 20 hours. Thorough ophthalmologic examinations during the occurrence of blurry vision did not reveal any significant change from baseline. The effect was described as a difficulty focusing at a far distance, without any change in intraocular pressure, anterior chamber angle, modification of the visual field, color vision, or fundus. Blurred vision was associated in one case with a reduced near visual acuity, and in 2 cases with a reduced amplitude of accommodation, but not associated with alteration of far visual acuity, refraction, or tear film. The mechanism of telithromycin-

induced visual blurring appears related to a delay in accommodation, but this does not explain the finding in older patients, who have decreased accommodative ability and who should therefore be less affected by telithromycin.

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

In the foreign post-marketing database of approximately 4 million exposures as of October 2003 (available prior to US approval) there were 414 telithromycin-associated visual adverse events reported by 316 patients. (See Appendix C for review of the foreign post-marketing reports of visual AE.) More events occurred in younger, female patients. Adverse events referable to vision were the most common post-marketing signal and comprised 34% (316/937) of all patients with any reported post-marketing complaint. Some of these patients treated with Ketek described significant disability/incapacity as a result of visual blurring. The majority of these cases were temporary, lasting on the order of hours to a few days. Onset of visual adverse events in the post-marketing database was not predictable, occurred at any time during treatment, and did not show permanent effects albeit in incomplete reports. For patients who experience visual problems, the Ketek package insert states that patients should not drive or engage in hazardous activities. Additional information provided as a Phase 4 commitment to further characterize visual complaints has recently been submitted but is still under review.

C. QT effects, drug-drug interactions, and special populations

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

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

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

In a careful review of foreign post-marketing data as of October 2003, there were a total of 101 cardiac adverse events reported by 86 patients. The majority of these events were either cardiac events occurring in older patients with pre-existing cardiac disease or symptoms, such as palpitations or tachycardia, occurring as part of a non-cardiac multi-symptom event. QT interval prolongation often results in cardiac events outside the setting of the type of medical monitoring necessary to identify them, and because these events may degenerate into non-distinct ventricular fibrillation, it is often difficult to identify potential drug-related QT toxicity in the post-marketing setting. Despite these limitations, review of these post-marketing data does not indicate any unusual cardiac safety signal for telithromycin.

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

D. Exacerbation of Myasthenia Gravis

There were no AE reports related to myasthenia gravis in the phase 3 clinical trials. However, the foreign post-marketing AE reports submitted prior to US approval included several reports of telithromycin-associated exacerbations of myasthenia gravis. There were six reports of life-threatening respiratory events. (See Appendix C Foreign Post-Marketing Safety for details of these AE.) Based on this information, the package insert included a warning about the potential for life-threatening AE in patients with myasthenia gravis.

IV. SUMMARY OF OVERALL EFFICACY

A. Acute Bacterial Exacerbation of Chronic Bronchitis

In the original NDA submission, there were two clinical trials submitted as evidence of efficacy for ABECB. These were multi-center, randomized, double-blind, active-controlled studies of telithromycin 800 mg once daily for 5 days. These studies were designed as non-inferiority studies evaluating clinical outcomes in telithromycin and comparator patients at a test-of cure (TOC) visit 17-24 days after the start of treatment. Investigators assessed patients as cure or failure based on symptoms, peak expiratory flow rates, and requirement for subsequent treatment. Study 3003 was performed outside the United States, and used amoxicillin/clavulanate 500/125 mg PO TID for 10 days as the comparator. Study 3007 was performed in the US and Canada, and used cefuroxime axetil 500 mg PO BID for 10 days as the comparator. The studies were similar in overall design, with the exception that study 3003 focused on patients with COPD (98% of patients met protocol definition for history of COPD versus 50% of patients in Study 3007).

The clinical outcomes for telithromycin and comparator patients at the TOC visit are shown in the following table. These results were considered substantial evidence of efficacy for telithromycin in the ABECB indication, based on demonstration of non-inferiority.

<u>FDA Analysis of ABECB Clinical Responses at the TOC Visit</u>

	Telithromycin 5-Days					Comparators 10-Days			2-sided 95% Confidence Interval
		N	Cure	%		N	Cure	%	
PPc Population									
Study 3003	115	99	86.1	AMC	112	92	82.1		(-6.4%, 14.3%)
Study 3007	140	121	86.4	CXM	142	118	83.1		(-5.8%, 12.4%)
MITT Population									
Study 3003	160	130	81.3	AMC	160	125	78.1		(-6.3%, 12.6%)
Study 3007	182	142	78.0	CXM	191	138	72.3		(-3.5%, 15.1%)

AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil

Bacteriological success (eradication or presumed eradication) was a secondary endpoint of the ABECB studies. Bacteriological success rates in the per-protocol bacteriological population were calculated at the TOC visit. In Study 3003, bacteriological success was reported in 69.2% (27/39) for telithromycin, compared to 70% (21/30) for amoxicillin/clavulanate. In Study 3007, bacteriological success was reported in 80% (20/25) for telithromycin, compared to 78.6% (22/28) for amoxicillin/clavulanate. Bacteriological success rates for telithromycin varied between trials.

The bacteriological success rates at the TOC visit by pre-therapy pathogen are provided in the following table. This table combines results from Study 3003 and 3007. Of note, the bacteriological success rate for telithromycin against *H. influenzae* is lower than for comparator. The small numbers available do not allow for statistically meaningful conclusions regarding efficacy against individual pathogens.

FDA Analysis of Bacteriological Success at TOC Visit by Pre-Therapy Pathogen from Combined Studies 3003 and 3007

All Pathogens	**Telithromycin** n/N %	**Comparators** n/N %
TOTAL	**54/70 (77.0%)**	**53/68 (77.9%)**
S. pneumoniae	13/14 (92.8%)	9/12 (75.0%)
H. influenzae	15/25 (60.0%)	15/17 (88.2%)
H. parainfluenzae	5/6 (83.3%)	0/1 (0.0%)
M. catarrhalis	10/10 (100.0%)	14/16 (87.5%)
S. aureus	2/2 (100.0%)	2/3 (66.6%)
Other	9/13 (69.2%)	13/19 (68.4%)

At the end of the first review cycle, the only concern regarding efficacy of telithromycin for the treatment of ABECB was the lower eradication rate for *H. influenzae* for telithromycin versus the comparators. This was noted by the review team and at the 1st advisory committee for Ketek (April 2001). The first approvable letter for Ketek (June 2001) noted that for ABECB, "Your

current application regarding *H. influenzae* and *M. catarrhalis* is insufficient due to low numbers of isolates."

An additional ABECB study was submitted in the 2nd review cycle (July 2002) for Ketek. Study 3013 was an international (including US), double-blind, randomized, active-controlled trial of telithromycin 800 mg once daily for 5 days. Clarithromycin 500 mg PO BID for 10 days was used as the comparator. Clinical outcome was assessed at the TOC visit on days 17-21 after the start of treatment.

The following table summarizes the clinical outcome rates by treatment group for the clinical per-protocol and modified intent-to-treat populations in the new study.

FDA Analysis of ABECB Clinical Responses at the TOC Visit

	Telithromycin 5-Days					**Comparator 10-Days**			**2-sided 95% Confidence Interval**
		N	**Cure**	**%**		**N**	**Cure**	**%**	
PPc Population									
Study 3013	225	193	85.8	CLA	231	206	89.2		(-10.0%, 3.1%)
MITT Population									
Study 3013	270	224	83.0	CLA	282	236	83.7		(-7.3%, 5.9%)

CLA= Clarithromycin

Bacteriological success rates (eradication or presumed eradication) are reported by pre-therapy pathogen in the following table. The bacteriological success rate for telithromycin against *H. influenzae* is higher than that seen in the original NDA submission. It also increases the number of *S. pneumoniae* and *M. catarrhalis* isolates.

FDA Analysis of Bacteriological Success at TOC Visit by Pre-Therapy Pathogen from Study 3013

All Pathogens	**Telithromycin**		**Comparators**	
	n/N	**%**	**n/N**	**%**
S. pneumoniae	10/13	(76.9%)	7/7	(100%)
H. influenzae	27/35	(77.1%)	30/36	(83.3%)
M. catarrhalis	17/19	(89.5%)	17/18	(94.4%)
S. aureus	2/4	(50.0%)	4/6	(66.6%)

The Clinical Studies section of the Ketek package insert describes the results of all three

ABECB studies, along with the bacteriological success rates for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* for all three combined studies.

B. Acute Bacterial Sinusitis

Three studies were submitted for Ketek in support of the ABS indication. All of the studies were submitted and reviewed in the 1st review cycle for Ketek. Each of the studies is somewhat different in design.

Study 3002 was a multi-center, double-blind, dose comparison (5 vs. 10 days) trial of patients with acute maxillary sinusitis. This study was conducted in Europe. Patients were enrolled based on clinical signs and symptoms and radiologic findings of complete opacification or air-fluid level; all patients had sinus puncture performed at baseline for bacteriological diagnosis. In this study, patients were randomized to receive either 5 or 10 days of telithromycin (800 mg once daily); there was no active comparator in this trial.

Study 3005 was a randomized, double-blind, active-control trial comparing telithromycin for 5 days, telithromycin for 10 days, and amoxicillin/clavulanate 500/125 mg PO TID for 10 days in patients with ABS. This was an international study including US patients. Patients were enrolled based on clinical signs and symptoms and radiographic findings. Sinus puncture was not required for study entry. The daily dose of telithromycin (800 mg once daily) was the same in all telithromycin-treated patients, regardless of the duration of telithromycin treatment.

Study 3011 was a randomized, double-blind, active-control trial comparing telithromycin 800 mg once daily for 5 days and cefuroxime axetil 250 mg PO BID for 10 days. This was an international study including US patients. Patients were enrolled based on clinical signs and symptoms and radiographic findings. Patients at designated centers had sinus puncture performed at baseline for bacteriological diagnosis. There was no 10-day telithromycin treatment arm in this trial.

The following table summarizes the FDA analysis of clinical outcomes at the TOC visit for the defined populations. The TOC visit was scheduled for days 17 to 24. Clinical outcomes (cure, fail, or indeterminate) at the TOC visit were assigned based on resolution or improvement in clinical findings, no worsening of radiological findings, and no need for subsequent antimicrobial treatment during the study.

FDA Analysis of ABS Clinical Responses at the TOC Visit

	Telithromycin 5-Days					**Comparators 10-Days**			**2-sided 95% Confidence Interval**
		N	**Cure**	**%**		**N**	**Cure**	**%**	
PPc Population									
Study 3002[1]	123	112	91.1	TEL 10-D	133	121	91.0		(-7.7%, 7.9%%)

Study 3005	146	110	75.3	AMC	137	102	74.5	(-9.9%, 11.7%)
Study 3011	189	161	85.2	CXM	89	73	82.0	(-7.1%, 13.4%)
MITT Population								
Study 3002	167	138	82.6	TEL 10-D	168	147	87.5	(-13.1%, 3.3%)
Study 3005	201	140	69.7	AMC	202	138	68.3	(-8.2%, 10.9%)
Study 3011	240	193	80.4	CXM	116	84	72.4	(-2.2%, 18.2%)

1 Study 3002 compared two dosing regimens of KETEK (5 days vs. 10 days).
TEL 10-D = telithromycin 10-Days, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil

In the PPc population, efficacy rates differed between studies for telithromycin treatment. The higher clinical response rates in Study 3002 might possibly be related to treatment bias, since it was known that all subjects received telithromycin (whether for 5 or 10 days). On the other hand, the lower response rates in Study 3005 are more difficult to assess without microbiological confirmation of ABS. However, the lower rates were seen in both the telithromycin and comparator patients.

The following tables show the clinical outcomes by baseline pathogen in patients receiving 5 days of telithromycin or comparator in the two active controlled studies (3005 and 3011). Although baseline sinus puncture was not performed routinely in Study 3005 it was performed in a few patients. In study 3002, the clinical outcomes for patients treated with 5 days of telithromycin at the test-of-cure visit were comparable to the results in the following tables. In the MITT population treated with 5 days of telithromycin in study 3002, clinical outcomes were 29/37 (78.4%) patients with *S. pneumoniae*, 15/16 (93.8%) for patients with *H. influenzae*, 7/8 (87.5%) for patients with *M. catarrhalis*, and 5/6 (83.3%) for patients with *S. aureus*.

FDA Analysis of Pathogen Specific Cure Rates in the MITT Population

Organism	**Telithromycin 5 days**	**Comparator**
S. pneumoniae	33/40 (82.5%)	17/21 (81.0%)
H. influenzae	37/43 (86.0%)	15/18 (83.3%)
M. catarrhalis	9/9 (100%)	7/8 (87.5%)
S. aureus	9/10 (90%)	2/3 (66.7%)

FDA Analysis of Pathogen Specific Cure Rates in the PPc Population

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

The following table shows outcomes for patients with *S. pneumoniae* grouped by penicillin and/or erythromycin resistance. The table includes patients treated with either 5 days or 10 days of telithromycin. The table shows that outcomes for telithromycin-treated patients do not appear different for erythromycin-susceptible and erythromycin-resistant strains of *S. pneumoniae*. Across sinusitis studies, there were 10 patients with PRSP isolated in the 5-day treatment groups. The clinical success rate in this group was 80% (8/10). There were 4 patients with PRSP isolates in the cefuroxime axetil group in study 3011, and all were considered cures.

FDA Analysis of Outcomes in ABS due to *S. pneumoniae* by resistance pattern in telithromycin-treated patients (PPb population, 3 studies combined)

Study #	**Outcome – Cured**					
	Pen-S	**PRSP**	**Ery-S**	**Ery-R**	**Pen-S + Ery-S**	**PRSP+ Ery-R**
3002	32/37 (86.5%)	**3/3 (100%)**	30/34 (88%)	**7/8 (87.5%)**	30/34 (88%)	**3/3 (100%)**
3005	2/2 (100%)	**1/1 (100%)**	2/2 (100%)	**1/1 (100%)**	2/2 (100%)	**1/1 (100%)**
3011	10/12 (83%)	**7/9 (77.8%)**	9/11 (82%)	**10/12 (83.3%)**	9/11 (82%)	**5/7 (71.4%)**
TOTAL	44/51 (86.3%) *12 mixed* (10/12, 83%)*	**11/13 (84.6%)** ***2 mixed (2/2, 100%)***	41/47 (87%) *12 mixed 9/12 (75%)*	**18/21 (85.7%)** ***5 mixed (5/5, 100%)***	41/47 (87%) *11 mixed (10/11, 91%)*	**9/11 (82%)** ***2 mixed (2/2, 100%)***

Overall, these studies were considered to provide substantial evidence of efficacy for telithromycin in the treatment of ABS due to *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The results of the comparative studies are described in the Clinical Studies section of the Ketek package insert. As noted in the second approvable letter (January 2003), no specific labeling for ABS due to penicillin-resistant or macrolide-resistant *S. pneumoniae* was permitted, because there is not sufficient evidence of the clinical relevance of penicillin or macrolide resistance in this disease to support a separate claim for resistant strains of *S. pneumoniae*.

C. Community-Acquired Pneumonia

The most studies were conducted in support of the claim for CAP. In the original NDA submission (February 2000), there were three comparative trials three open-label, non-comparative trials. The following table provides a description of the CAP clinical studies submitted in the 1st review cycle. Of particular note, one of the comparative studies (3009) was terminated early because the comparator (trovafloxacin) had been associated with hepatic toxicity in post-marketing. Because of this early termination, the study lost significant power to demonstrate non-inferiority.

CAP Trials in the Original NDA

STUDY	**DESIGN**	**TREATMENT**	**DAYS**	**N****	**GEOGRAPHIC REGION**
Pivotal Comparative Studies					

3001	Multicenter, double-blind, randomized, active-controlled, comparative, 2-arm parallel group	Telithromycin 800 mg po qd Amoxicillin 1000 mg po tid	10 d 10 d	404	Argentina, Australia, Austria, Finland, France, Germany, Hungary, South Africa, Spain, Sweden, UK, New Zealand, Uruguay
3006	Multicenter, double-blind, randomized, active-controlled, comparative	Telithromycin 800 mg po qd Clarithromycin 500 mg po bid	10 d 10 d	416	USA, Canada, Argentina, Chile
3009*	Multicenter, double-blind, randomized, active-controlled, comparative	Telithromycin 800 mg po qd Trovafloxacin 200 mg po qd	7 - 10 d 7 - 10 d	204	USA, Canada, South Africa
Supportive Non-Comparative Studies					
3000	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 - 10 d	240	Argentina, Australia, Austria, Belgium, Finland, France, Germany, Hungary, Israel, New Zealand, Norway, South Africa, Sweden
3009OL	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 – 10 d	212	South Africa
3010	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 d	418	USA, South America, South Africa, Canada

** This study was terminated prematurely because of safety concerns with the comparator, trovafloxacin.*
*** Number of patients in MITT population*

These studies all involve similar procedures for study entry, monitoring and assessment of outcome. Enrollment is based on the presence of signs and symptoms of pneumonia with X-ray confirmation. Microbiological testing includes sputum culture, blood cultures, and serology for atypical pathogens. Some studies included urinary antigen testing for *S. pneumoniae*. Clinical outcome is based on resolution or significant improvement of signs and symptoms of pneumonia, no need for additional antimicrobial treatment, and at least no worsening of X-ray findings. The TOC visit is conducted 1-2 weeks after the end of study drug treatment. The following table shows the clinical outcomes at the TOC visit for the various studies.

FDA Analysis of CAP Clinical Responses at the TOC Visit

	Telithromycin	**Comparators**	**2-sided 95% Confidence Interval**

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

TEL = telithromycin, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin
** Non-comparative studies*

The following table shows clinical and bacteriological outcomes by pathogen for telithromycin-treated patients with CAP in the comparative and open-label clinical studies listed above. While outcomes for patients with penicillin- or erythromycin-resistant strains of *S. pneumoniae* were evaluated, they are not shown here because they represent only a portion of the total experience with multi-drug resistant *S. pneumoniae* (MDRSP) described later in this section.

FDA Analysis of CAP Bacteriological Eradication and Clinical Cure Rates at the TOC Visit for Telithromycin-Treated Patients in the PPb* Population

Causative pathogen	**Bacteriological eradication**				**Clinical cure**		
		N	**Cure**	**(%)**	**N**	**Cure**	**(%)**
S. pneumoniae	174	166	(95.4)	174	165		(94.8)

H. influenzae	105	94	(89.5)	105	95	(90.5)
M. catarrhalis	30	27	(90.0)	30	26	(86.7)
S. aureus	19	15	(78.9)	19	15	(78.9)

** PPb = Bacteriological Per-protocol Population*

The following table provides clinical outcomes at the TOC visit for patients in the PPc population with atypical pathogens.

FDA Analysis of Clinical Outcome at the TOC Visit for CAP Patients with Atypical Pathogens Based on FDA Diagnostic Criteria

Pathogen	**Telithromycin**				**Comparator**		
		N	**Cure**	**%**	**N**	**Cure**	**%**
Chlamydophila pneumoniae	34	32	94.1	18	17		94.4
Mycoplasma pneumoniae	31	30	96.8	19	18		94.7

The analysis of CAP studies in the original NDA also included an evaluation of clinical outcomes at the TOC visit for specific subgroups of interest. These subgroup analyses are shown in the following table. Of note, outcomes did not appear to differ significantly from the overall population based on these factors. Because the studies were evaluations of outpatient treatment for mild-to-moderate CAP, most patients in the clinical trial had Fine Score of Class I or II.

FDA Subgroup Analysis of Clinical Outcome at the TOC Visit for CAP Patients by Age, Fine Score, and Pneumococcal Bacteremia

Subgroup	**Telithromycin**		
		N	**cure**	**%**
Per protocol (overall)	1132	1046	92.4
Age (years)			
<65	978	907	92.7
>65	154	139	90.3
Pneumococcal Bacteremia	47	43	91.5
Fine Score			
Class I	554	517	93.3
Class II	403	368	91.3
Class III or greater	175	161	92.0

At the end of the first review cycle, these studies were considered to provide substantial evidence of the efficacy of Ketek in the treatment of mild-to-moderate CAP. In April 2001, at the first advisory committee meeting for Ketek, the committee voted 7 to 3 in favor of approval of Ketek for treatment of CAP. However, the committee also voted 3 to 7 against a specific claim for penicillin-resistant *S. pneumoniae* (PRSP) and erythromycin-resistant *S. pneumoniae* (ERSP) in CAP, because the available data were not considered to be sufficient. In June 2000, the FDA issued an approvable letter for the Ketek application, citing insufficient data for the

treatment of CAP due to PRSP and ERSP, and recommended further studies targeting resistant pathogens.

In the 2nd review cycle, additional CAP studies were submitted in July 2002 to provide additional cases of CAP due to PRSP and ERSP. The sponsor submitted two additional US studies as described in the following table.

CAP Trials Submitted in the 2nd Review Cycle

Study	Design	Treatment Regimen	Duration	N	Geographic Region/ No. of Study Sites
4003	Multicenter, Double-blind, Randomized, Active-controlled, Comparative, 3-arm parallel group	Telithromycin 800 mg qd Telithromycin 800 mg qd Clarithromycin 500 mg bid	5 days 7 days 10 days	187 191 181	Argentina, Brazil, Canada, Chile, Germany, South Africa, Spain, United Kingdom, USA
3012	Multicenter, Open-label, Non-comparative	Telithromycin 800 mg qd	7 days	538	Argentina, France, Mexico, South Africa, Spain, USA

The results of these studies were consistent with the outcomes for the CAP trials in the original NDA submission. For example, the clinical cure rates at the TOC visit in the PPc population in Study 4003 were 88.8% (143/161) for patients who received 7 days of telithromycin and 91.8% (134/146) for clarithromycin patients. However, the CAP review in the 2nd review cycle focused on outcomes for patients with CAP due to PRSP and ERSP.

The table on the following page provides the FDA analysis of clinical cure rates for telithromycin-treated CAP patients from all the CAP studies with drug-resistant *Streptococcus pneumoniae* isolated from baseline cultures (sputum and/or blood). Clinical outcome was assessed at the TOC visit. A total of 49 cases (MITT population) were identified where PRSP and/or ERSP were isolated. The table separates patients by resistance patterns. Results are shown for both the per-protocol and modified intent-to-treat populations. Of note, 16/28 (57.1%) PRSP isolates were also resistant to erythromycin.

In cases with PRSP isolates (regardless of erythromycin resistance), the clinical cure rate was 16/19 (84.2%) in the per-protocol group and 20/28 (71.4%) in the MITT population. For cases with ERSP isolates (regardless of penicillin resistance), the clinical cure rate was 25/29 (86.2%) in the per-protocol group and 29/37 (78.4%) in the MITT population.

In the comparative studies (3001, 3006, 3009, and 4003), there were 7 comparator-treated patients with drug-resistant *S. pneumoniae* identified in baseline cultures. One amoxicillin-treated CAP patient had ERSP isolated from sputum. The isolate was susceptible to penicillin. She was considered cured at the TOC visit. One clarithromycin-treated CAP patient had PRSP identified in baseline cultures. The isolate was susceptible to erythromycin. He was considered

cured at the TOC visit. Five CAP patients with ERSP were treated with clarithromycin in the comparative trials. At the TOC visit, 4/5 were considered cured. However, one of the clinical cures was noted to have a recurrence of pneumonia at a later follow-up visit.

FDA Analysis of Clinical Cure Rates in Patients with Drug-Resistant *Streptococcus pneumoniae* by Resistance Pattern

Study Population/ Resistance mechanism	**Telithromycin 800 mg qd**		
		N	**Cure %**
PPb Population			
PRSP Only*	8	8	100
ERSP Only**	18	17	94.4
Both PRSP and ERSP***	11	8	72.7
MITT Population			
PRSP Only*	12	9	75.0
ERSP Only**	20	18	90.0
Both PRSP and ERSP***	16	11	68.8

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≤ 1 µg/ml*
*** Patients with isolates whose penicillin MIC ≤ 2 µg/ml and erythromycin MIC > 1 µg/ml*
**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC > 1 µg/ml*

Outcomes for CAP patients with pneumococcal bacteremia due to drug-resistant strains were also evaluated. In CAP patients with bacteremia due to PRSP (regardless of erythromycin resistance), the clinical cure rate was 5/7 in the per protocol group and 5/10 in the MITT population. For bacteremia due to ERSP (regardless of penicillin resistance), the clinical cure rate was 8/10 in the per protocol group and 8/11 in the MITT population.

The information described for CAP due to PRSP and ERSP were presented to the advisory committee on January 8, 2003. The information was considered sufficient evidence of efficacy to support claims for PRSP and ERSP (close votes of 7 to 5 in favor of each). In part, the split vote represented a balance of the need for antibiotics active against PRSP, and alternatives to fluoroquinolones with concerns regarding the small number of cases, and concerns regarding the relevance of resistance to other antibiotics. In the 2nd approvable letter, issued on January 24, 2003, the Division stated there was not sufficient evidence of the clinical relevance of macrolides-resistant *Streptococcus pneumoniae* as an entity distinct from penicillin-resistant *Streptococcus pneumoniae*.

At the time of approval (April 2004), the applicant and FDA had performed analyses to evaluate resistance to other antibiotics in these PRSP/ERSP strains. The following tables show the clinical outcomes for patients with CAP due to antibiotic-resistant *S. pneumoniae* in the PPc and MITT populations for telithromycin-treated patients in the controlled and open-label clinical studies. Since cross-resistance to multiple antibiotics is common for PRSP/ERSP isolates, the same patient may be included in multiple rows on these tables. In these analyses, 56 CAP patients had isolates resistant to one or more antibiotics that were treated with telithromycin. Only 8 of the isolates were resistant to a single drug (all erythromycin). Of the remaining isolates, which are all MDRSP by definition, the clinical cure rate was 38/47 (80.1%). One

subject was considered to have an indeterminate outcome, and was excluded from the analyses.

Clinical Outcome for patients with CAP due to antibiotic-resistant *S. pneumoniae* treated with telithromycin – MITT Population

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

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

Clinical Outcome for patients with CAP due to antibiotic-resistant *S. pneumoniae* treated with telithromycin – PPc Population

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

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

For labeling purposes, the FDA defined the term multi-drug resistant *Streptococcus pneumoniae* [MDRSP], which included isolates known as PRSP, and were isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, trimethoprim/sulfamethoxazole, and tetracyclines. The clinical outcomes for telithromycin-treated patients with CAP due to MDRSP were 91.9% (34/37) in the PPc population, and 80% (40/50) in the MITT population. The cure rates of bacteremic CAP patients with MDRSP were 84.6% (11/13) in the PPc population and 68.8% (11/16) in the MITT population. In April of 2004, Ketek was approved with an indication for community-acquired pneumonia (of mild to moderate severity) including CAP due to MDRSP. The Clinical studies section included a description of the outcomes in the controlled and uncontrolled clinical studies, the outcomes by pathogen, and the above information for evaluable patients with MDRSP isolates.

V. SUMMARY OF AGENCY CONCLUSIONS AND ACTION

Ketek was approved in April of 2004 for the indications of CAP, ABS, and ABECB. The data that provided substantial evidence of safety and efficacy included the following:

- Multiple comparative studies of community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and tonsillopharyngitis: These comparative studies were the basis for efficacy claims in

CAP, ABS, and ABECB. The studies also served as the basis for safety claims, providing information on the rates of adverse effects seen with Ketek compared to other antibiotics used for these indications.

• Non-comparative studies of CAP with Ketek: In addition to the comparative CAP studies, these studies of CAP provided additional data on outcomes in patients with CAP due to multi-drug resistant *Streptococcus pneumoniae*. These non-comparative studies also provide safety data on the use of Ketek in the treatment of CAP.

• Phase 1 Visual studies: These studies of high-doses of telithromycin were performed to study the mechanism of the visual effects of Ketek.

• There were multiple other phase 1 studies evaluating the pharmacokinetics of Ketek. These studies included food effect studies, drug interaction studies, QT prolongation, and studies of the pharmacokinetics of Ketek in patients with renal or hepatic impairment.

• Foreign post-marketing data were also evaluated as part of the assessment of safety to identify rare serious adverse effects of Ketek (e.g., serious hepatic, visual, cardiac adverse effects) based upon post-marketing reports from other countries where Ketek was approved. (See discussion of Center-wide briefing above.)

The FDA could not rely on the results of the large safety study (Study 3014) that was conducted to evaluate the frequency of adverse effects with Ketek (e.g., hepatic, visual, cardiac adverse events) because of systematic failure of the trial monitoring program to detect data integrity problems when they clearly existed.

At the time of approval in April 2004, the Ketek product label included safety information in the product label including Warning information about the potential to prolong the QT interval, exacerbations of myasthenia gravis, and antibacterial drug standard labeling on pseudomembranous colitis; Precautions on visual disturbances and hepatic dysfunction including increased liver enzymes and hepatitis; information on drug interactions; data on adverse reactions from the clinical trials program and data from post-marketing adverse event reports from experience marketing the product outside of the United States. The Ketek product label contains no information on Study 3014, since the Agency could not rely upon it, as noted above.

VI. POST-MARKETING INFORMATION FOR KETEK

In the post-marketing period, there was still ongoing activity with Ketek. A new 300 mg tablet formulation was approved specifically for use in patients with severe renal impairment. A labeling supplement to add information about interactions between telithromycin and oral anticoagulants was also approved. The applicant also submitted a labeling supplement to add palpitations, pancreatitis, and syncope to the post-marketing adverse event reports. **Appendix E** contains the medical officer review for this supplement. It provides a summary of selected cases of loss of consciousness associated with use of Ketek. This included four reports from Japan of motor vehicle accidents occurring following these syncopal events. Because of these reports, the label was modified to add a precaution about syncope and strengthen precautions for driving or use of heavy machinery.

The FDA continued to receive sporadic reports of hepatic adverse effects, and periodic re-

evaluation of hepatic events included a consult review approximately one year after marketing of Ketek began in the U.S. This review noted that cases of visual and hepatic adverse effects are consistent with those seen prior to approval in worldwide experience and as described in the current labeling.

A separate document from the Office of Surveillance and Epidemiology, dated November 9, 2006, documents the additional work in the post-marketing assessment of adverse effects associated with telithromycin. This work included a re-assessment of hepatotoxicity, continuing through the time period after reports were published noting hepatotoxicity associated with the use of Ketek.

The re-assessment also included a data mining analysis of post-marketing adverse effects reported for Ketek and other drugs (macrolides, cephalosporins, quinolones, amoxicillin/ clavulanate, and acetaminophen). This document, included in **Appendix F**, provides an overview of adverse effects reported in post-marketing for the selected drugs.

The Division of Anti-Infective and Ophthalmology Products, in conjunction with the Office of Surveillance and Epidemiology and following consultation with Special Government Employee experts in hepatology, added a Warning about acute hepatic failure to the product label. The labeling changes also strengthened the Warning for exacerbation of myasthenia gravis. The revised labeling was approved on June 29, 2006. A copy of the current labeling for Ketek is included in **Appendix G**.

VII. APPENDICES

A. Summary of Microbiology

Telithromycin is a semisynthetic antibacterial belonging to the ketolide family of antimicrobials, within the macrolide-lincosamide-streptogramin (MLS_B) class. It inhibits bacterial protein synthesis by action at the 23S rRNA of the 50S ribosomal subunit.

Telithromycin has in vitro activity against Gram-positive bacteria, fastidious Gram-negative bacteria, some anaerobes, and atypical pathogens (*Chlamydophila pneumoniae*, *Legionella pneumonia*, and *Mycoplasma pneumoniae*). It is bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes*. Telithromycin is bactericidal against penicillin- or erythromycin-susceptible and -resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It has little or no activity against methicillin-resistant *S. aureus* or methicillin-resistant coagulase-negative staphylococci.

MIC_{90} ranges for target pathogens are as follows:

S. pneumoniae (including penicillin- and erythromycin-resistant stains): 0.25 μg/mL

H. influenzae (β-lactamase-negative: 2 μg/mL; β-lactamase-positive: 4 μg/mL)

M. catarrhalis (including β-lactamase-positive strains): 0.5 μg/mL

S. aureus (methicillin and erythromycin susceptible isolates): 0.3 μg/mL

S. pyogenes (erythromycin-susceptible: 0.06 μg/mL; erythromycin-resistant: 8 μg/mL)

Telithromycin has *in vitro* activity against some strains of *S. pneumoniae* that carry the *mef*E

and *erm*B genes, as well as against strains of *S. pyogenes* that do not carry *erm*B. Increased MIC_{90}s have been observed in strains of *S. pyogenes* that carry *erm*B.

No data are available with regard to synergism or antagonism with other antimicrobials. Telithromycin has been shown to have a post-antibiotic effect ranging from approximately 1 to 8 hours at 10x MIC against the pathogens of interest. A decrease in pH from 7 to 5.5 increases the telithromycin MIC for *S. pneumoniae* by approximately 15-fold. Increasing inoculum size from 10^4 to 10^5 cfu/mL does not affect the MIC. If the inoculum size is 10^7 or greater, the telithromycin MIC for *S. pneumoniae* goes up approximately 2 to 4-fold.

B. Liver Function Test Abnormalities in Phase 3 Studies

Changes in ALT by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and Total Bilirubin at Baseline, Integrated Controlled Database

	On-Therapy								**Post-Therapy[a]**		**Late Post-Therapy[b]**	
Changes in ALT	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 544		N= 418		N= 378		N= 337		N= 295		N= 221	
	n	(%)	N	(%)	N	(%)	N	(%)	n	(%)	n	(%)
<ULN	478	87.9	376	90.0	328	86.8	304	90.2	272	92.2	203	91.9
>ULN to ≤2xULN	55	10.1	38	9.1	45	11.9	29	8.6	19	6.4	15	6.8
>2 to ≤3xULN	7	1.3	3	0.7	5	1.3	3	0.9	3	1.0	3	1.4
>3 to ≤5xULN	4	0.7	0	0	0	0.0	1	0.3	1	0.3	0	0.0
>5 to ≤8xULN	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0
>8xULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	31		35		197		116		280		232	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Changes in AST by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and Total Bilirubin at Baseline, Integrated controlled database

	On-Therapy				**Post-Therapy[a]**	**Late Post-Therapy[b]**
Changes	**Ketek**	**Comp**	**Ketek**	**Comp**	**Ketek**	**Comp**

in AST												
	N=545		N= 418		N= 379		N= 337		N= 295		N= 221	
	n	(%)	N	(%)	N	(%)	N	(%)	n	(%)	n	(%)
<ULN	487	89.4	387	92.6	354	93.4	326	96.7	276	93.6	203	91.9
>ULN to ≤2xULN	52	9.5	27	6.5	22	5.8	11	3.3	18	6.1	17	7.7
>2 to ≤3xULN	3	0.6	2	0.5	2	0.5	0	0.0	0	0.0	0	0.0
>3 to ≤5xULN	3	0.6	2	0.5	1	0.3	0	0.0	1	0.0	0	0.0
>5 to ≤8xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5
>8xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	30		35		196		116		280		232	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Changes in T. Bili by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline, Integrated controlled database

	On-Therapy								**Post-Therapy[a]**		**Late Post-Therapy[b]**	
Changes in T. Bili	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 521		**N= 403**		**N= 359**		**N= 326**		**N= 281**		**N= 214**	
	n	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**
<ULN	517	99.2	401	99.5	355	98.9	320	98.2	280	99.6	212	99.1
>ULN to ≤2xULN	3	0.6	2	0.5	4	1.1	4	1.2	1	0.4	1	0.5
>2 to ≤3xULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	1	0.5
>3 to ≤5xULN	1	0.2	0	0	0	0.0	1	0.3	0	0.0	0	0.0
>5 to ≤8xULN	0	0.0	0	0	0	0.0	1	0.3	0	0.0	0	0.0
>8xULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	54		50		216		127		294		239	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Changes in ALT by Visit in Controlled Phase 3 Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline, Integrated controlled database

	On-Therapy								Post-Therapy[a]		Late Post-Therapy[b]	
Changes in ALT	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 1316		**N= 1038**		**N= 1114**		**N= 928**		**N= 511**		**N= 422**	
	n	**(%)**	**N**	**(%)**	**n**	**(%)**	**N**	**(%)**	**N**	**(%)**	**n**	**(%)**
<ULN	1234	93.8	995	95.9	1047	94.0	854	92.0	479	97.3	394	93.4
>ULN to ≤2xULN	78	5.9	39	3.8	64	5.7	71	7.7	26	5.1	26	6.2
>2 to ≤3xULN	3	0.2	4	0.4	2	0.2	1	0.1	4	0.8	0	0.0
>3 to ≤5xULN	0	0.0	0	0.0	1	0.1	2	0.2	1	0.2	2	0.5
>5 to ≤8xULN	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
>8xULN	1	0.1	0	0.0	0	0.0	0	0.0	0	0	0	0.0
Number of patients lacking lab data for visit	69		59		271		169		874		675	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Changes in AST by Visit in Controlled Phase 3 Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline, Integrated controlled database

	On-Therapy								Post-Therapy[a]		Late Post-Therapy[b]	
Changes in AST	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 1315		**N= 1041**		**N= 1112**		**N= 926**		**N= 511**		**N= 422**	
	n	**(%)**	**N**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**
<ULN	1260	95.8	1004	96.7	1087	97.8	901	97.3	498	97.5	402	95.3
>ULN to ≤2xULN	53	4.0	33	3.2	22	2.0	23	2.5	8	1.6	20	4.7
>2 to ≤3xULN	1	0.1	1	0.1	1	0.1	0	0.0	3	0.6	0	0.0
>3 to ≤5xULN	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
>5 to ≤8xULN	1	0.1	1	0.1	2	0.2	1	0.1	1	0.2	0	0.0

>8xULN	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Number of patients lacking lab data for visit	70		59		273		171		874		675	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Changes in T. Bili by Visit in Controlled Phase 3 Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline, Integrated controlled database

	On-Therapy								**Post-Therapy[a]**		**Late Post-Therapy[b]**	
Changes in T. Bili	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 1293		**N= 1010**		**N= 1092**		**N= 912**		**N= 498**		**N= 416**	
	n	**(%)**	**N**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**
<ULN	1285	99.4	1007	99.7	1075	98.4	905	99.2	492	98.8	414	99.5
>ULN to ≤2xULN	8	0.6	3	0.3	17	1.6	7	0.8	6	1.2	2	0.5
>2 to ≤3xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
>3 to ≤5xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
>5 to ≤8xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
>8xULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	92		87		293		185		887		681	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

C. Safety Review from 3rd Cycle – Executive Summary and Review Excerpts of Foreign Post-Marketing for Myasthenia Gravis, Hepatic and Visual Adverse Events

D. Summary of Phase 1 Visual Effects Studies

Two Phase 1 studies (Studies 1059 and 1064) of the visual effects of telithromycin were submitted by the Applicant.

Study 1059: "Mechanism of blurred vision induced by HMR 3647 [telithromycin] at single supraclinical doses (2400 mg) versus therapeutic single dose (800 mg) in a younger and older population of healthy subjects"

Methods
This study was a single-center, randomized, placebo-controlled, double-blind, single-dose, three-way crossover study with a one-week washout period between treatments. Two groups of healthy adult subjects were studied:

Group I: 15 subjects 18 to 40 years of age with normal uncorrected vision

Group II: 15 subjects 50 to 64 years of age with presbyopia

Approximately equal numbers of males and females were to be enrolled in each group. Each subject received three treatments: telithromycin 800 mg, telithromycin 2400 mg, and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

Plasma concentrations and amounts of drug in tears were determined at baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration. Eye examinations were performed at the following times:

At baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration:

- Far and near visual acuity for each eye
- Accommodation (near point and amplitude) using a Clark rule
- Pupil diameter
- Refraction
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At baseline and between 4 and 8 hours after study drug administration:

- Visual field with Amsler's grid
- Color vision
- Slit lamp examination (lids, cornea, lens, iris, fundus)
- Intraocular pressure using air puff tonometry method

Results
Thirty subjects were enrolled, 15 in each group. Group I had 7 male and 8 female subjects; mean age was 26 years (range 18 to 37 years). Group II had 6 male and 9 female subjects; mean age was 56 years (range 49 to 63 years). All subjects completed the study.

Plasma pharmacokinetic parameters were similar between groups. Measured amounts of telithromycin in tears were somewhat higher in Group I. Four of 15 subjects (3 females, 1 male) in Group I and no subjects in Group II reported blurred vision. These reports are summarized in the following table.

Subject	Age/ gender	Dose (mg)	Time post dose	Duration	Intensity	Description/symptoms	Eye exam	Other AE
2	18/F	2400	4 h	2 h	mild	blurred vision/far vision	No change	None
6	21/F	2400	6 h	1 h	mild	blurred vision/instability of far vision both eyes	No change	Nausea
9	25/F	2400	3 h	1 h	mild	blurred vision/difficulty focusing eyes, short latent period needed to focus for far vision	No change	Nausea
11	25/M	2400	3 h	30 min	mild	blurred vision/short latent period to focus for near and far vision	No change	Nausea, diarrhea

All cases occurred at the 2400 mg dose of telithromycin. Blurring developed 3 to 6 hours following drug administration, lasted 30 minutes to 2 hours, and was described as mild in intensity. Far vision was affected in all four subjects and near vision as well in one. The investigator reported that two subjects had a short latent period to focus, either for far vision alone or for both far and near vision. Three subjects had concurrent nausea, and one also had diarrhea. There was no concurrent eye pain, discomfort, foreign body sensation, photophobia, stinging, burning, or tearing. During the episodes of blurred vision, there were no changes in visual acuity, refraction, pupillary diameter, color vision, visual fields, and slit lamp examinations. There were no decreases in amplitude of accommodation and no increases in intraocular pressure. These subjects reported no blurred vision and there were no changes observed in their eye examinations after they received either the 800 mg dose of telithromycin or placebo. No changes from baseline eye examinations were observed in any of the subjects in Groups I or II following receipt of study medication.

Study 1064: "Assessment of ophthalmological safety of telithromycin at supraclinical dose (2400 mg) in healthy subjects"

Methods

This was a single-center, randomized, placebo-controlled, double-blind, single-dose, two-way crossover study with a one-week washout period between treatments. Twenty-four healthy adult subjects were studied. At least 35% were to be between 50 and 64 years of age. All subjects were required to have normal uncorrected far vision; a correction for near vision was acceptable for the older subjects. Each subject received two treatments: telithromycin 2400 mg and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

Plasma concentrations were determined at baseline and at 1, 2, 3, 4, and 6 hours after study drug administration. Eye examinations were performed at the following times:

At screening: uncorrected and corrected visual acuity, fixation disparity test, refraction, intraocular pressure, color vision, slit lamp examination, fundus photography

At baseline, 3 hours, and 7 days after study drug administration:

- Far and near visual acuity for each eye
- Contrast sensitivity function for each eye

- Refraction
- Continuous recording of accommodation and pupil size using an autorefractor
- Slit lamp examination (lids, cornea, lens, iris, anterior chamber angle, fundus)
- Color vision
- Visual field threshold automated testing
- Tear film stability using a tearscope
- Intraocular pressure using air puff tonometry method
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At end of study: fundus photography

Results

Twenty-four subjects were enrolled; 18 were 18 to 49 years of age, and 6 were 50 to 64 years of age. Thirteen males and 11 females were enrolled. All subjects completed the study.

Telithromycin mean C_{max} was 5.11 mg/L (range 2.84-7.81 mg/L) and median t_{max} was 3 hours (range 1-4 hours). These values are consistent with those obtained with this dose in previous studies. Twelve (50%) of the 24 subjects (7 females, 5 males) reported blurred vision, 10 of 12 (83%) in the 18 to 49 year age group and 2 of 6 (33%) in the 50 to 64 year age group. These reports are summarized in the following table.

Subject	Age/gender	Treatment	Time post dose	Duration	Intensity

1	55/M	Telithromycin	1h 10m	2h 50m	Moderate
2	20/F	Telithromycin	3h 20m	18h 29m	Moderate
5	21/M	Telithromycin	1h 18m	4h 27m	Mild
6	19/M	Telithromycin	5h	0h 53m	Mild
10	30/F	Placebo	3h	18h 55m	Mild
10	30/F	Telithromycin	2h 50m	3h 15m	Moderate
13	34/M	Telithromycin	3h 6m	1h 14m	Mild
15	40/F	Telithromycin	3h 7m	2h 43m	Mild
17	54/F	Telithromycin	3h 5m	2h 25m	Mild
18	22/M	Telithromycin	1h 25m	20h 20m	Mild
21	47/F	Telithromycin	2h	5h 30m	Moderate
23	27/F	Telithromycin	2h 55m	3h 55m	Mild
24	41/F	Telithromycin	2h 35m	2h 40m	Mild

All 12 subjects reported blurred vision following administration of telithromycin; one subject also reported blurred vision following administration of placebo. Blurring developed 1 to 5 hours after dosing (median 3 hours) and lasted for a median of 2h 50 min. Three subjects (two

telithromycin, one placebo) had a duration of blurring of 18 to 20 hours; the exact duration is uncertain because these subjects reported blurring at bedtime and were questioned the following morning. Narrative detail about the episodes of blurred vision is limited. The blurring was most commonly described as difficulty focusing, particularly on distant objects. The intensity was described as mild for eight subjects and moderate for four. Several subjects had concurrent dizziness, nausea, and diarrhea. One subject reported photophobia, one reported ocular discomfort, and one had diplopia; there were otherwise no concurrent eye complaints.

Eye examinations following drug administration demonstrated no consistent findings attributable to telithromycin, either in those reporting blurred vision or in those exposed but without blurring. There were no changes from baseline in visual fields, color vision, intraocular pressure, anterior chamber angle, or pupil diameter. One subject with blurring had impairment of near visual acuity, decrease in amplitude of accommodation, and impaired near-to-far reaction and response times. Continuous recording of accommodation in all subjects revealed no consistent changes in reaction or response times following drug administration. Tear film stability was reduced in three subjects with blurring and in three without blurring (one following telithromycin, two following placebo). Slit lamp examination was abnormal in one subject with blurring, who had a corneal defect believed possibly due to eye rubbing; all remaining slit lamp examinations were normal.

E. Labeling Supplement Review – Post-Marketing Reports of Syncope

F. Data Mining

G. Current Ketek (Telithromycin) Product Label (Last Modified June 29, 2006)